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Methodologies for the Synthesis of Functionalized Naphthols and Progress toward the Total Synthesis of Vineomycinone B_2 Methyl Ester and Actinophyllic Acid

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Methodologies for the Synthesis of Functionalized Naphthols and Progress toward the Total Synthesis of Vineomycinone B_2 Methyl Ester and Actinophyllic Acid

by

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Methodologies for the Synthesis of Functionalized Naphthols and Progress toward the Total Synthesis of Vineomycinone B_2 Methyl Ester and Actinophyllic Acid

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Chi-Li Chen, Ph. D.

The University of Texas at Austin, 2007

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A general and efficient methodology for the synthesis of *cis*-2-substituted-1,2-dihydro-1-naphthols and 2-substituted-1-naphthols from oxabenzonorbornadienes was developed. The procedure involved the sequential palladium-catalyzed ring opening of oxabenzonorbornadienes with aryl or vinyl halides followed by oxidation of the intermediate dihydronaphthols with IBX. The scope of the palladium-catalyzed coupling was extended to a variety of halides such as aryl iodides and bromides bearing both electron-withdrawing and -donating groups, vinyl bromides, and glycal iodides. Oxidation of *cis*-2-substituted-1,2-dihydro-1-naphthols using IBX led to 2-substituted-1-naphthols in good to excellent yields. Application of such methodologies successfully led to a Group II *C*-aryl glycoside model.

The double intramolecular benzyne–furan cycloadditions and naphthyne–furan cycloadditions were developed. In the model studies, furans and the reacting benzynes or naphthynes were linked with silicon tethers and, thus, the regiochemistry of Diels–Alder cycloadditions could be controlled. Two different tactics for converting the resultant oxabenzonorbornadienes to substituted anthrarufins were demonstrated. The first method entails the initial cleavage of the silicon tethers followed by regioselective ring opening of the oxabenzonorbornadienes and oxidation of the central ring giving the target anthrarufin, whereas the second features the regioselective ring opening of the oxabenzonorbornadienes followed by protiodesilylation and oxidation. Application of the chemistry demonstrated in the model double benzyne-furan cycloadditions successfully led to a total synthesis of vineomycinone B_2 methyl ester. This strategy enables the rapid assembly of the glycosyl-substituted aromatic frameworks of complex *C*-aryl glycoside antibiotics from simple starting materials.

We propose an oxidative Mannich reaction for the synthesis of an indole natural product, actinophyllic acid. The synthesis features the selective oxidation of a C3-alkyl indole followed by intramolecular nucleophilic addition of an enol ether to build a bicylcic framework. This approach may provide a convergent access to the skeleton of actinophyllic acid. Currently, we have prepared indole **5.77**, and continuing efforts will be focused on the formation of azepino[4,3-*b*]indole **5.78** and the key oxidative Mannich reaction.

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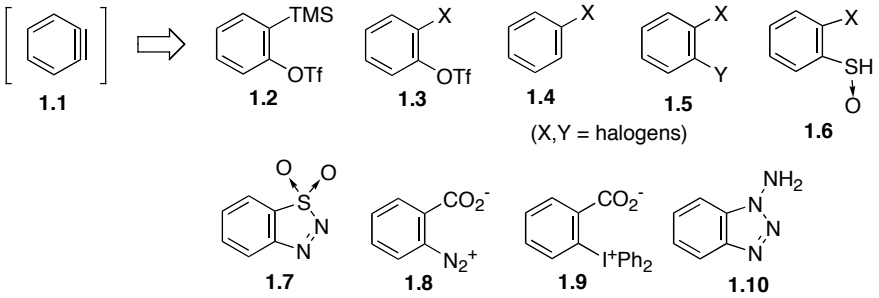
Chapter 1. Aryne Chemistry in Organic Synthesis

1.1 INTRODUCTION

The first evidence for the existence of an aryne was reported 100 years ago; however, it took several decades until Roberts, Huisgen, and Wittig obtained definitive evidence for the existence of these reactive intermediates.[1] Arynes are formed when the loss of two adjacent *ortho* substituents from an aromatic ring results in the formation of a triple bond. The preferred linear geometry of the triple bond is deviated to 120° angles by the ring, rendering the aryne extraordinarily unstable and reactive, even at low temperature. Many studies on the generation and reactions of arynes have been undertaken.[2] Examples of representative aryne precursors reported include *o*-trimethylsilylphenyl triflate (**1.2**), *o*-halophenyl triflate (**1.3**), halobenzene (**1.4**), *o*-dihalobenzene (**1.5**), *o*-halophenylsulfoxide (**1.6**), benzothiadiazole *S*,*S*-dioxide (**1.7**), benzenediazonium-2-carboxylate (**1.8**), diphenyliodonium-2-carboxylate (**1.9**), and aminobenzotriazole (**1.10**) (Figure 1.1).[3]

Figuar 1.1

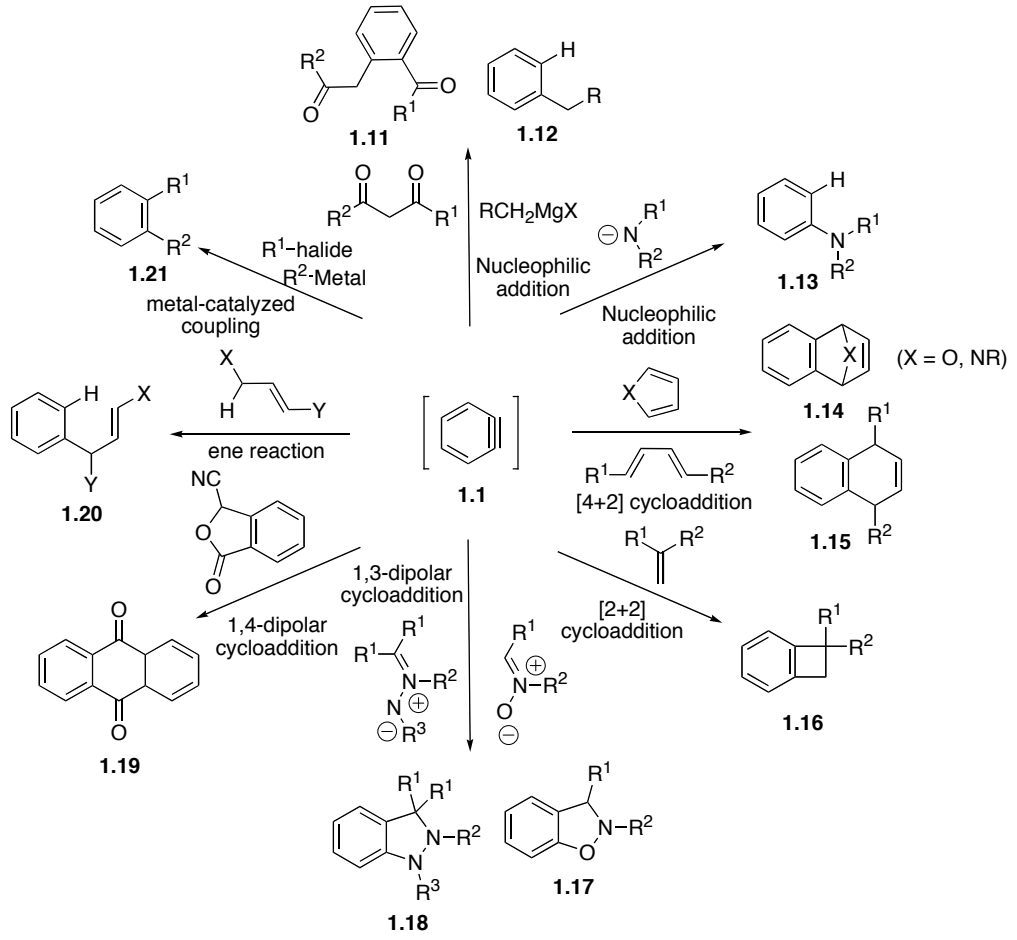


1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 1.10

Arynes have been recognized as potential intermediates for the synthesis of a wide variety of highly functionalized aromatic compounds, materials and natural products.[2] Their reactions can be divided into three groups: nucleophilic addition to

arynes, transition metal-catalyzed reaction of arynes and pericyclic reaction of arynes (Figure 1.2).[2]

Figure 1.2



The nucleophilic coupling reactions with arynes have received considerable attention.[2] Owing to their low-lying LUMO, arynes are very electrophilic, and even neutral nucleophiles readily add to them. The most interesting nucleophiles are carbanions and nitrogen-, oxygen- and sulfur-centered nucleophiles. Transition metal-catalyzed reactions of arynes have been widely studied, and most reactions involve palladium catalysts. The pericyclic reactions can be divided into several categories,

including the Diels–Alder reaction, [2 + 2] cycloaddition, 1,3-dipolar cycloaddition, 1,4-dipolar cycloaddition, and the ene reaction. In particular, the use of arynes in the Diels–Alder process with a wide range of dienes constitutes an important synthetic tool. Regioselective reaction with asymmetric arynes has been exploited in the construction of complex organic molecules. Multi-component couplings with arynes are very attractive approaches from a synthetic standpoint for generating diverse aromatic molecules. These reactions will be discussed in more detail in this chapter.

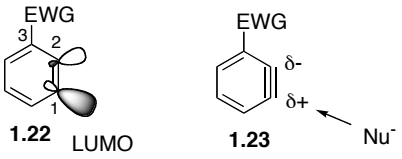
1.2 NUCLEOPHILIC ADDITION TO ARYNES

1.2.1 Regioselectivity in Nucleophilic additions

The reactions of arynes with various nucleophiles have been thoroughly reviewed.[2] These nucleophiles include carbanions, as well as nitrogen-, oxygen- and sufur-centered nucleophiles. The addition of nucleophiles to arynes is highly regioselective when the benzyne bears an electron-withdrawing group at C3 position.

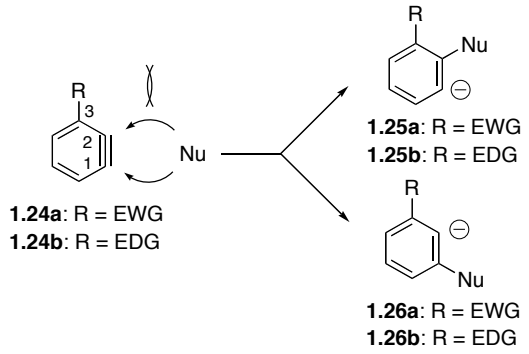
Substituents present on an aryne can orient the incoming nucleophile through electronic and steric effects.[2b,4,5] Electronically, the "inductive effect" is more important than the resonance effect since the reacting benzyne orbital is orthogonal to the ring π-system. The inductive effect "polarizes the aryne triple bond" and "influences the stabilization of the negative charge" in the transition state. C3 electron-withdrawing substituents such as alkoxy, amino, phenyl and vinyl groups, within aryne species behave inductively to enhance electrophilicity at C1 relative to C2 by "polarization" of the triple bond, directing nucleophilic additions at C1 position (Figure 1.3).

Figure 1.3



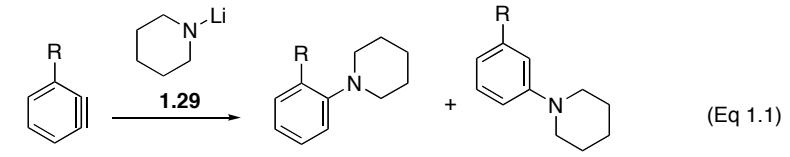
The reaction tends to provide the "more stable" carbanion intermediate **1.25** or **1.26** in the transition state (Scheme 1.1). For the aryne **1.24a** with an electron-withdrawing substituent at C3 positon, the nucleophilic addition to C1 position of the aryne is preferred because the resultant negative charge can be stabilized to a greater extent in the transition state leading to **1.26a** due to the inductive effect of the substituent. On the other hand, the steric repulsive interaction is minimal for the attack at the less hindered *meta* addition. Consequently, when an electron-withdrawing substituent is present at C3 of an aryne, lower *ortho* : *meta* product ratio may be obtained.

Scheme 1.1



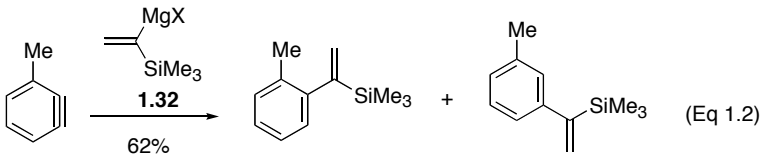
The electronic and the steric effects operate in opposition to each other for aryne **1.24b** with a C3 electron-donating substituent, such as silyl groups.[2b] Electronically, inductive polarization by the substituent enhances electrophilicity at C2 position of the aryne, and the transition state corresponding to the *ortho* adduct **1.25b** is stabilized to some extent. However, C2 position is sterically more congested. With weak electron-

donating alkyl groups, the *ortho*:*meta* ratio is rarely greater than unity and can be much less if large substituents and nucleophiles are involved. For example, in the addition of lithium piperidide (**1.29**) to 3-methylbenzyne, this ratio is 1 : 2, whereas it is 1 : 24 in the addition to 3-isopropylbenzyne (Eq 1.1).[2b] In coupling of **1.27** with **1.32**, the *meta* isomer **1.33b** was the major product (Eq 1.2).[2b] This trend in favor of *meta* addition has been utilized for the synthesis of *meta*-substituted toluenes.



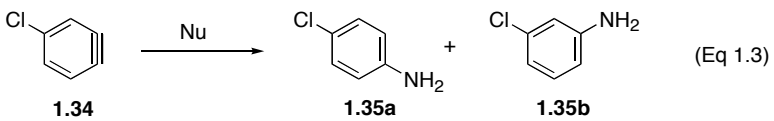
1.27: R = Me
1.28: R = i-Pr

R = Me, **1.30a/1.30b** = 1 : 2
R = *i*-Pr, **1.31a/1.31b** = 1 : 24



1.27 **1.33a** 9 : 91 **1.33b**

In reactions of C4 substituted benzynes, both the inductive and steric effects are less pronounced.[2b] The degree of selectivity is sensitive to nucleophilicity, the stronger nucleophiles being less selective. Weak nucleophiles, however, do show some positional selectivity. For example, the *para : meta* ratio in additions of amide ions to 4-chlorobenzyne **1.34** is near unity, but it is 4.9 for the addition of ammonia (Eq 1.3). It was suggested that in the transition state for the addition of weak nucleophiles the incipient bond is more developed, and the inductive stabilization derived from the substituent becomes more important.

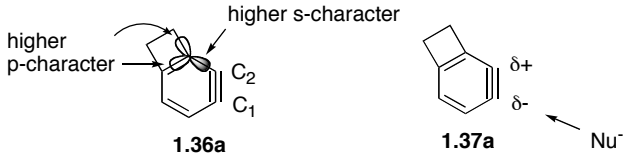


1.34 **1.35a** **1.35b**

Nu = $NaNH_2$, 1 : 1
Nu = NH_3, 4.9 : 1

In addition to C3 substituted arynes, Suzuki reported a four-membered ring fused to a benzyne, such as **1.36a**, has a directing effect for the reaction with nucleophiles (Figure 1.4).[5] The crucial factor for determining the regioselectivity resides in the four-membered ring. The C3 orbital with higher p-character bonds to the strained four-membered ring (see **1.36a**). Hence, the remaining C3 orbital has higher s-character with higher electronegativity bonding with C2, rendering C1 more electron-deficient (see **1.37a**). Therefore, regioselective reactions were observed upon treatment with nucleophiles. However, C3 orbital does not possess significant s-character for the benzyne with a larger fused ring and, thus, the regioselectivity dramatically decreased.

Figure 1.4



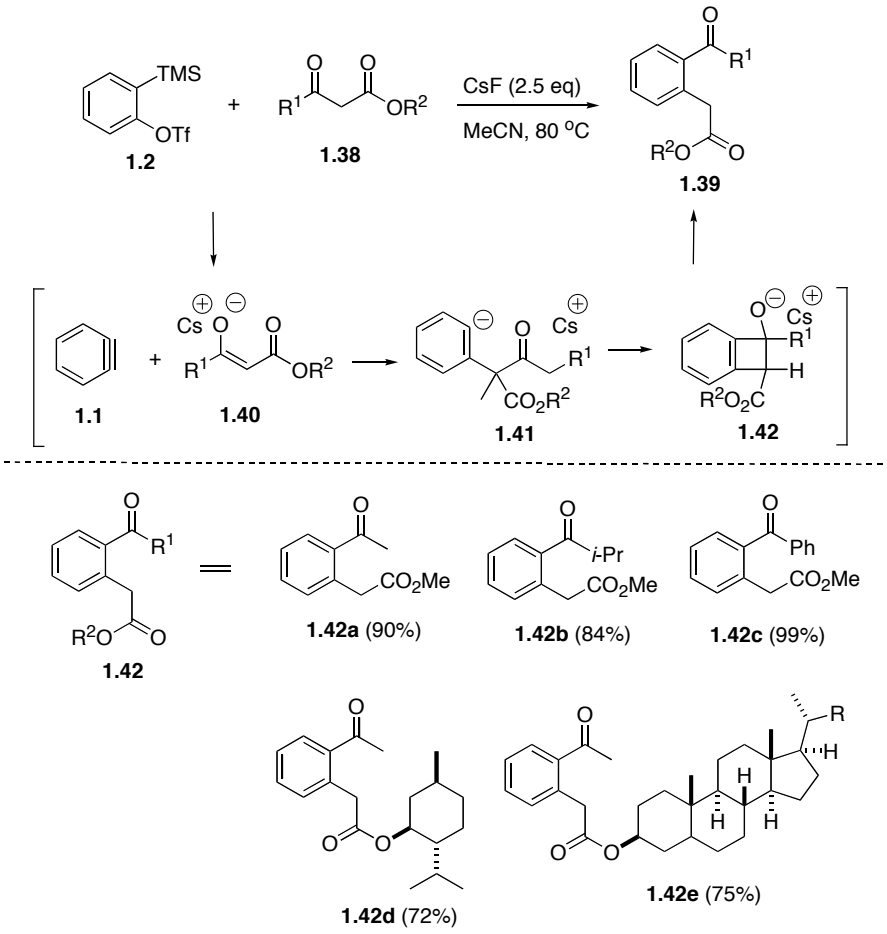
1.2.2 Addition of Carbon Nucleophiles to Arynes

In recent decades, the addition of carbon nucleophiles to arynes has been widely explored, and lithionitriles,[6] enolates,[7] β-ketoenolates,[8,9] isocyanides,[10] organocuprates,[6] Grignard reagents,[11,12] and organolithiums[6] are among the nucleophiles that have been investigated. Nucleophilic addition to the aryne followed by trapping of the resulting aryl anion with an electrophile has extended the scope of the aryne chemistry. This approach provides rapid access to highly functionalized arenes, isochroman-3-ones, anthraquinones, anthrone imines, isoquinolines, biphenyl-based phosphine ligands, tetralones and some antiobiotic nature products.[2] Two of the most recent representative

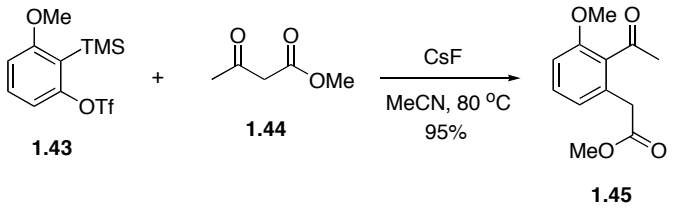
examples will be illustrated here.[9,12] They feature the aryne tandem coupling reactions that allow the formation of complex carbon skeletons in a single step. Application of these reactions has led to the total synthesis of amurensinine (+)-(**1.52**) and clavilactone B (**1.57**).

The addition of lithium malonates to benzynes was first studied by Guyot in 1977,[13] and was applied for the synthesis of dynemicine A precursor by Danishefsky in 1996.[14] A decade later, Stoltz extended the methodology to β-ketoenolates.[8,9] Stoltz reported a mild and efficient condition for the acyl-alkylation of arynes *via* a cascade process (Scheme 1.2).[8] *ortho*-Disubstituted products **1.39** were obtained upon treatment of *β*-ketoesters **1.38** with the benzyne precursor *o*-trimethylsilyl triflate (**1.2**) in the presence of CsF. The nucleophilic addition of β-ketoenolate **1.40**, generated from **1.38** under the basic condition, to benzyne **1.1** provided an aryl anion intermediate **1.41**, which underwent intramolecular nucleophilic addition at the carbonyl carbon atom followed by retro-aldo type elimination to give *ortho*-disubstituted products **1.39**.

Scheme 1.2



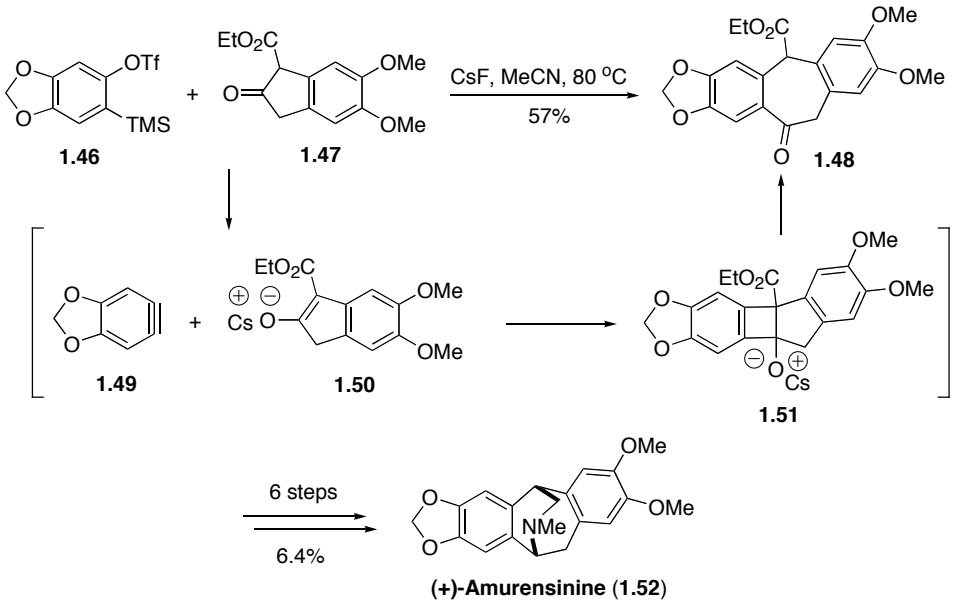
The regioselectivity of this reaction was also explored by Stoltz. The coupling of 3-methoxy benzyne precursor **1.43** with methyl acetoacetate **1.44** was completely regioselective to provide adduct **1.45** in excellent yield (Eq 1.4).[8] The high regioslectivity could be attributed to the inductive and steric effect as the discussion in Chapter 1.2.1.



(Eq 1.4)

The aryne/α-ketoester coupling followed by ring expansion was developed and used for the generation of the synthetically challenging polycyclic carbon framework of amurensinine (+)-**1.52** (Scheme 1.3).[9] The coupling of aryne precursor **1.46** and cyclic α-ketoester **1.47** in the presence of CsF gave good yield of ketoester **1.48**, which was then elaborated to form amurensinine (+)-**1.52**.

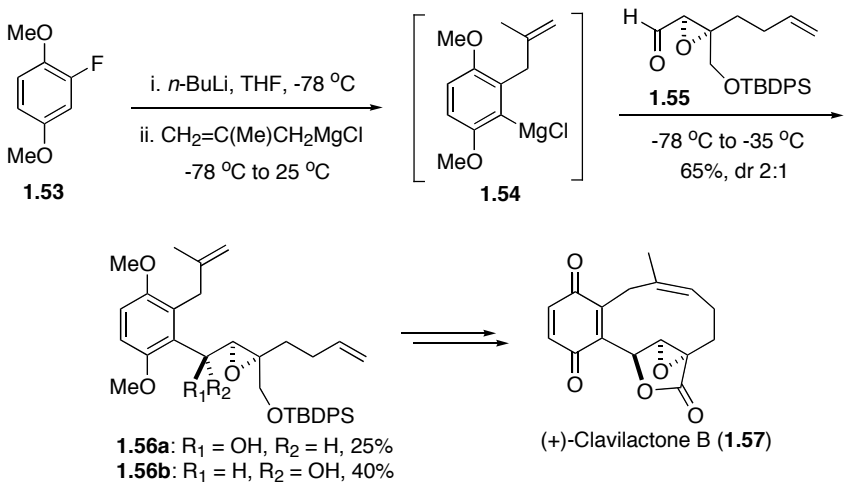
Scheme 1.3



Barrett reported the first asymmetric synthesis of clavilactone B (**1.57**) in 2006.[12] He employed a convergent three-component benzyne coupling and a ring closing metathesis to prepare the carbon skeleton of the molecule. Treatment of fluorobenzene **1.53** with *n*-BuLi at -78 °C gave an *o*-fluoroaryllithium intermediate (Scheme 1.4). Methylallyl Grignard was added, and the reaction was allowed to warm to room temperate during which time benzyne formation followed by Grignard addition generated the aryl Grignard species **1.54**. Epoxyaldehyde **1.55** was then added at -78 °C to provide two diasteromeric benzyl alcohols **1.56a** and **1.56b**. These two alcohols were converted

to clavilactone B (**1.57**) through a selective epimerization and ring closing metathesis.

Scheme 1.4

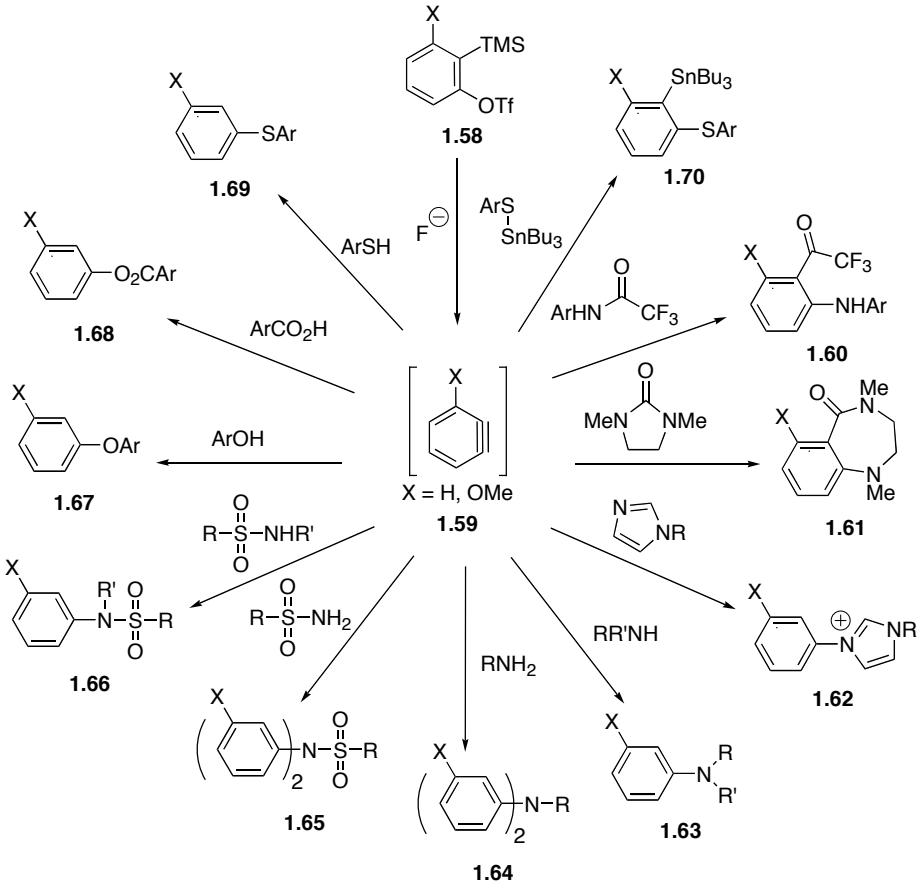


1.2.3 Addition of Nitrogen, Oxygen and Sulfur Nucleophiles to Arynes

Heteroatom nucleophilic addition to arynes is currently a very active research area in organic synthesis.[15] Numerous methods have been established that allow for the formation of highly functionalized arenes under the fairly mild conditions. For example, aryne **1.59**, which was generated from the reaction of silylaryl triflate **1.58** with fluoride ions, reacts with a variety of *N*-nucleophiles (amines, sulfonamides, carbamates, imidazoles, and imidazolidinone), *O*-nucleophiles (phenols and carboxylic acids), and *S*-nucleophiles (stannyl sulfides and phenyl thiols) to give the corresponding arenes (Scheme 1.5).[4,16] The regioselectivity of the nucleophilic addition to 3-methoxybenzyne is excellent. Reactions involving 3-methylbenzynes or 4-methoxybenzynes, however, give two isomers with poor regioselectivity. Monoarylated amines (**1.63**, R′ = H) and diarylated amines (**1.63**, R′ ≠ H) can be easily obtained from the coupling of **1.58** with

primary amines by simply controlling the ratio of the reactants.[4,16c,g] A variety of functional groups are compatible with the reaction conditions, including alkenes, alkynes, nitro groups, aldehydes, ketones, esters, and amides. Several examples have shown that aryl iodides, which are not compatible in the Pd-catalyzed *N*-arylations and *O*-arylations, readily tolerate these reaction conditions.[4,16c-d,f-g]

Scheme 1.5

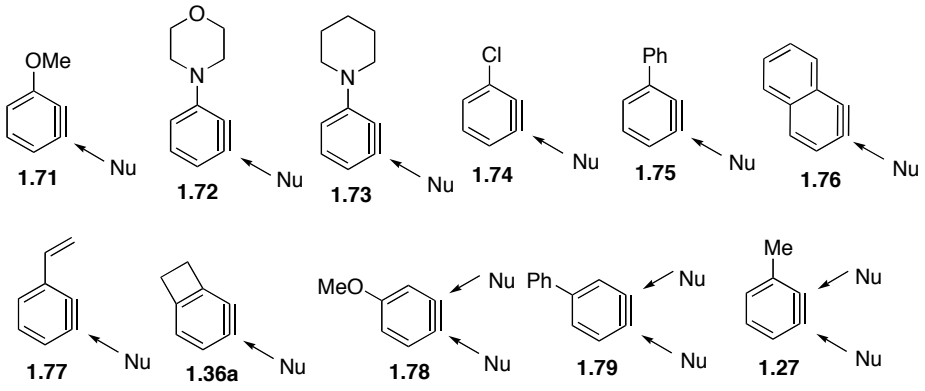


Despite the fact that Buchwald and Hartwig have demonstrated significant strategies for *N*-arylations and *O*-arylations,[17] there are still some limitations in these reactions. For example, (1) it is still difficult to prepare *N*-arylated sulfonamides using

transition-metal catalysts;[18] (2) phenols can smoothly be converted to diaryl ethers only if no strong electron-withdrawing group is present;[19] (3) the palladium-catalyzed coupling of aromatic carboxylic acids with aryl halides, and the carbonylation of aryl halides to generate the corresponding aryl esters are difficult;[20] (4) and most reaction conditions are fairly harsh and usually require high temperature. However, these limitations associated with the transition metal-catalyzed reactions can easily be solved by using aryne reactions as shown in Scheme 1.5.

Excellent regioselectivities are observed not only when C3 methoxy benzyne (**1.71**) is used, but also when benzyne possessing C3 amino, halo, phenyl, and vinyl groups (**1.72**-**1.77**), and benzyne (**1.36a)** with fused cyclobutane ring are employed (Figure 1.5).[21,5] However, both steric and electronic effects are less pronounced for 4-methoxybenzyne **1.78**, 4-phenylbenzyne **1.79** and 3-methylbenzyne **1.27**, resulting in the formation of a mixture of regioisomers.[16e-g]

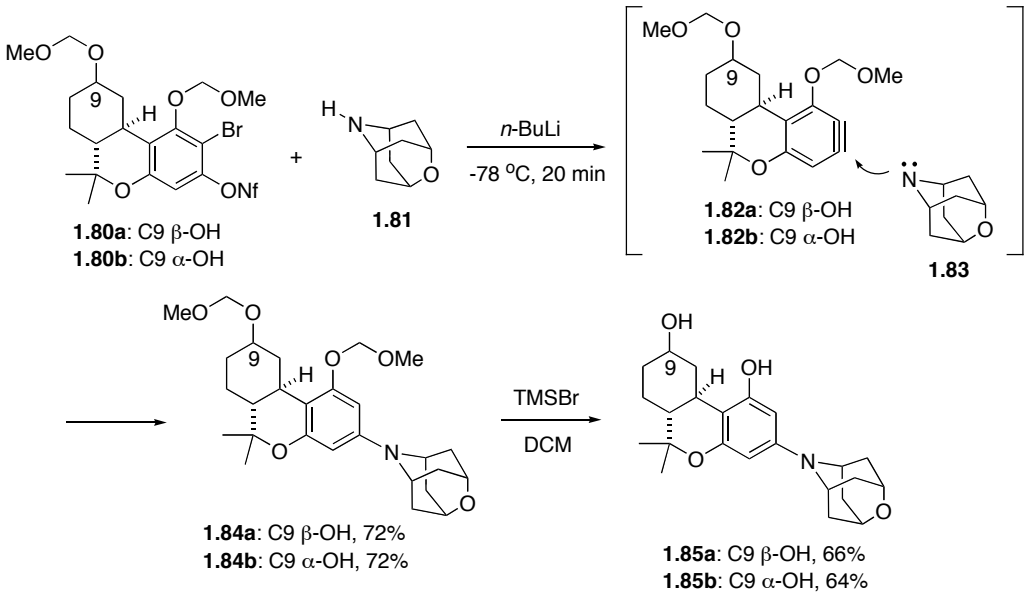
Figure 1.5



Several natural products and biological active analogs have been synthesized through heteroatom nucleophilic addition to arynes.[2] One of the most recent examples was the synthesis of oxaza adamantly cannabinoids (**1.85a**-**b**)[22] which represent a new

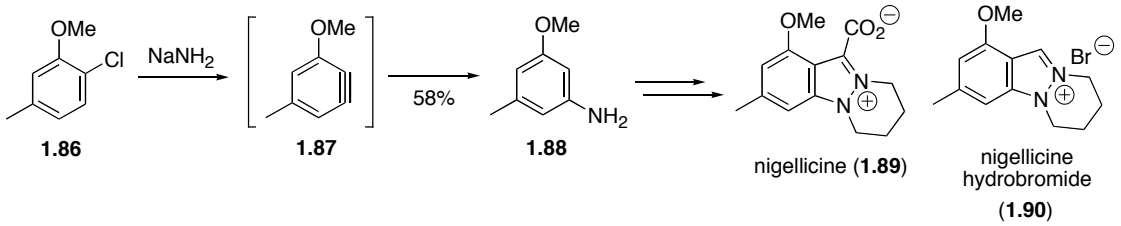
class of ligands for CB1 and CB2 receptors.[23] Treatment of bromononaflate **1.80a** and amine **1.81** in THF with *n*-BuLi provided aryne intermediate **1.82a**, which underwent nucleophilic addition with the adamantyl amide anion to provide cannabinoid **1.84a** as a single isomer in 72% yield (Scheme 1.6). This result indicates that the amide addition to the aryne is regiospecific. The process was repeated with **1.80b**, leading to **1.84b** in 72% yield. Methoxymethyl protecting groups were removed upon treatment with TMSBr[24] in dichloromethane to provide cannabinoids **1.85a** and **1.85b**.

Scheme 1.6



Nigellicine **1.89** and nigellicine hydrobromide **1.90**, two pyridazinoindazolium alkaloid natural products, were synthesized from precursor aniline **1.88** (Scheme 1.7).[25] Aniline **1.88** was formed *via* regioselective addition of an amide nucleophile to benzyne **1.87**, derived from deprotonation of aryl chloride **1.86**.

Scheme 1.7



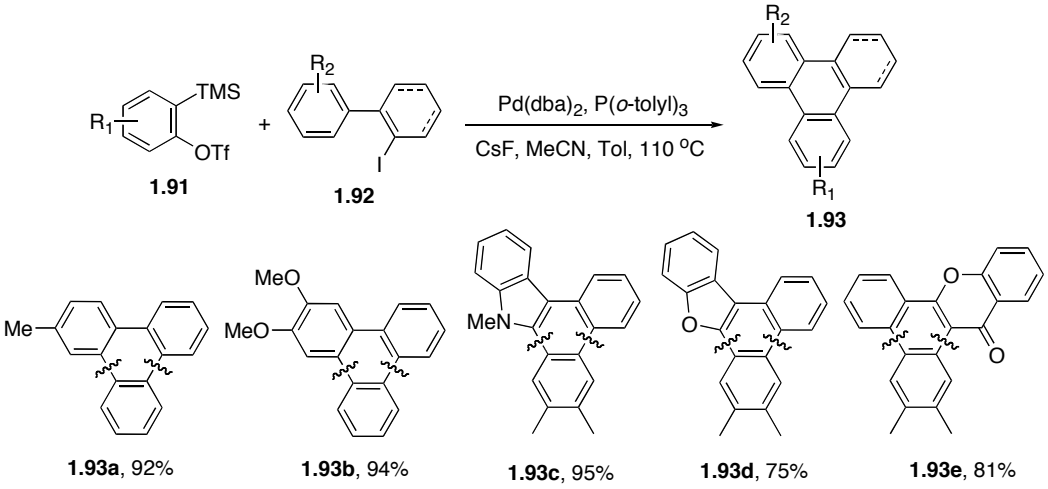
1.3 METAL-CATALYZED REACTION WITH ARYNES

The use of transition-metal catalysts such as palladium,[26] nickel[27] and gold,[28] in aryne chemistry has provided rapid and efficient access to diverse polycyclic aromatic hydrocarbons, *o*-functionalized arenes and some biological active products.[2] Among all of the transition metal-catalyzed reactions, palladium-catalyzed couplings have been extensively studied and reviewed in depth.[2] The feasibility of metal-catalyzed reactions with arynes can depend on three main reasons. (1) In the past, the synthetic applications of metal-catalyzed couplings with arynes were limited, owing to the lack of mild conditions for aryne generation and the need for stoichiometric amounts of metal catalysts in these reactions.[2] New methods for the generation of arynes under mild conditions have led to the exploration of metal-catalyzed aryne reactions. (2) The coordination of arynes to transition metals relaxes part of the aryne strain, possibly even resulting in a stable species. This concept can be supported from a wide variety of stable transition metal complexes (Ta, Zr, Re, Ti, Ni, Pt, Ru, Pd), that bear arynes as ligands.[2] (3) Aryne is a good carbometallation partner and allows for the formation of aryl-metal intermediates or metallacycles.[29] Metal-catalyzed cyclotrimerizations of arynes, co-cycloadditions of arynes with alkynes, cycloadditions of arynes with allenes or allyl derivatives, and carbonylative cycloadditions of arynes have been reviewed.[2] The focus

of this chapter will be on some recent interesting tandem coupling reactions.

Larock reported in 2005 a synthesis of fused polycyclic aromatics, employing the Pd-catalyzed carboannulation of arynes with substituted aryl or vinylic halides.[26] Aryl and vinylic halides **1.92** reacted with *o*-(trimethylsilyl)phenyl triflate **1.91** in the presence of palladium catalyst and cesium fluoride, to provide a number of heterocycles **1.93** in good yields (Scheme 1.8). These heterocyclic products included indoles, benzofurans and chromones.

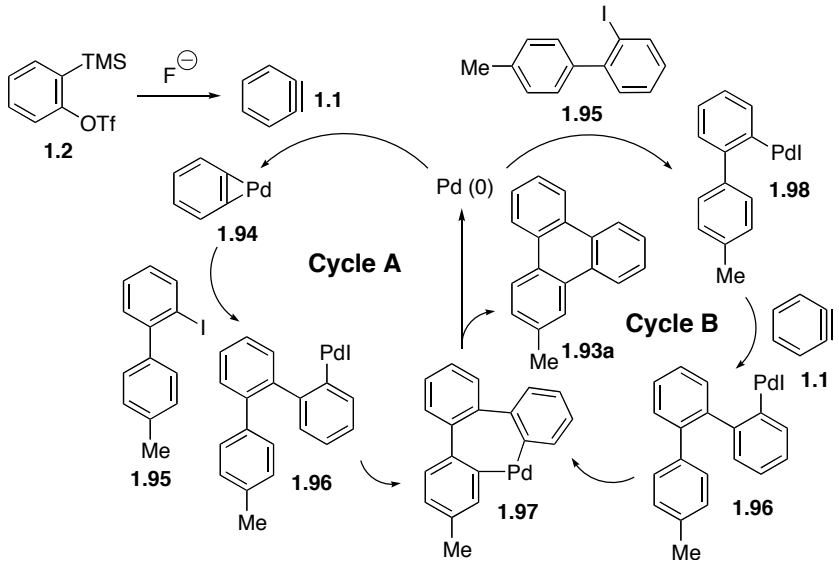
Scheme 1.8



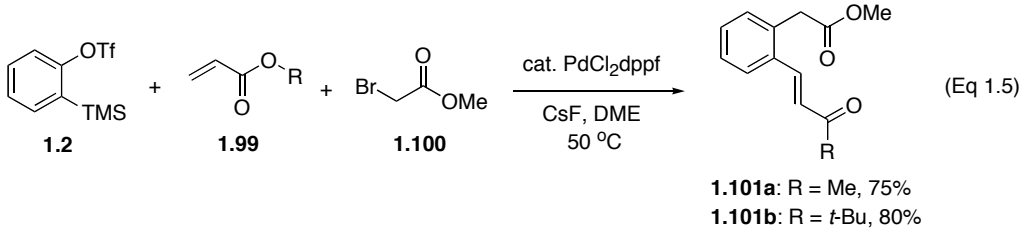
Larock suggested two possible mechanisms (cycles A and B) to account for these aryne annulation processes (Scheme 1.9).[26] The main difference between these two mechanisms is the Pd oxidative addition step. In cycle A, the Pd(0) complex initially undergoes oxidative cyclization with aryne **1.1** to generate palladacycle **1.94**.[30] Subsequent reaction with iodide **1.95** affords intermediate **1.96**, which undergoes intramolecular C-H activation to generate palladacycle **1.97**. Subsequent reductive elimination furnishes the observed annulation product **1.93a** and regenerates the Pd(0) catalyst. Cycle B involves oxidative addition of iodide **1.95** to Pd(0) to give

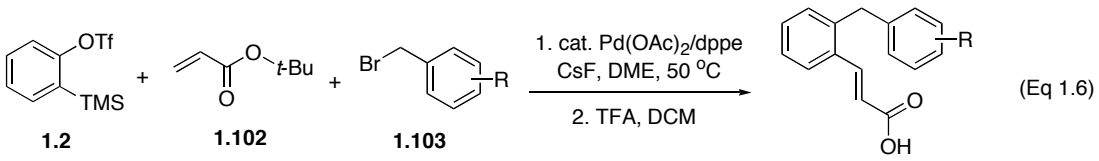
arylpalladium intermediate **1.98**, which reacts with aryne to afford intermediate **1.96**. C-H activation and subsequent reductive elimination provides product **1.93a**.

Scheme 1.9



In 2006, Greaney group reported a three-component coupling (TCC) reaction of benzyne based upon two successive intermolecular carbopalladation reactions.[31] The methodology provides quick and easy access to 1,2-functionalized arenes. The tandem coupling using $PdCl_2$dppf as a catalyst allowed for rapid combination of benzyne, alkyl acrylate **1.99** and methyl bromoacetate **1.100** to provide TCC products **1.101** in good yields (Eq 1.5). The coupling of *tert*-butyl acrylate **1.102** and benzyl bromide **1.103** in the presence of $Pd(OAc)_2$/dppe provided vinyl esters, and subsequent acid-catalyzed hydrolysis delivered carboxylic acids **1.104** in good yields over two steps (Eq 1.6).



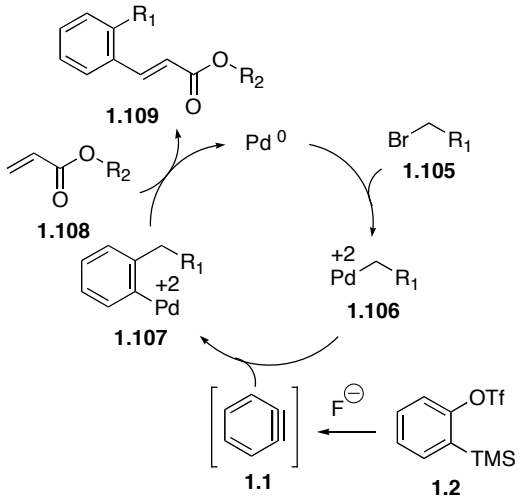


(Eq 1.6)

1.104a: R = *m*-Cl, 65%
1.104b: R = *m*-OMe, 62%
1.104c: R = *p*-CN, 89%
1.104d: R = *p*-CF_3, 67%

The mechanism is shown in Scheme 1.10. Oxidative addition of activated bromide **1.105** to Pd(0) generates organopalladium intermediate **1.106**, which undergoes carbopalladation with benzyne to give arylpalladium species **1.107**. Coupling was followed by an intermolecular olefin insertion with unsaturated ester **1.108**, and then β-H elimination to give 1,2-functionalized benzene **1.109**.

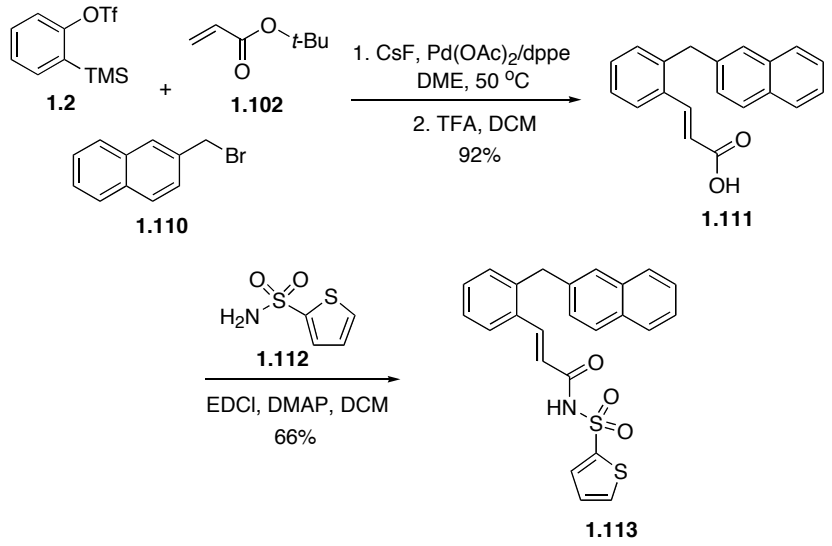
Scheme 1.10



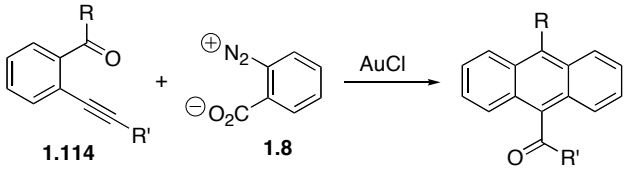
To demonstrate the TCC coupling for the rapid assembly of biologically active compounds, Greaney reported the synthesis of prostenoid EP3 receptor antagonist **1.113** recently published by Merck[32] (Scheme 1.11).[31] TCC coupling of naphthyl bromide **1.110** with *tert*-butyl acrylate **1.102** and benzyne, followed by acid-catalyzed hydrolysis provided unsaturated acid **1.111** in excellent yield. Coupling of acid **1.111** with

sulfonamide **1.112** then gave the EP3 antagonist **1.113** in 61% overall yield over three steps.

Scheme 1.11



Asao reported in 2006 a AuCl-catalyzed formal [4 + 2] benzannulation of *o*-alkynyl(oxo)benzenes **1.114** with benzenediazonium 2-carboxylate (**1.8**) to give anthracene derivatives **1.115** bearing a ketone group at the C9 position (Eq 1.7).[28] This is the first example of gold-catalyzed Diels-Alder reaction with benzyne.



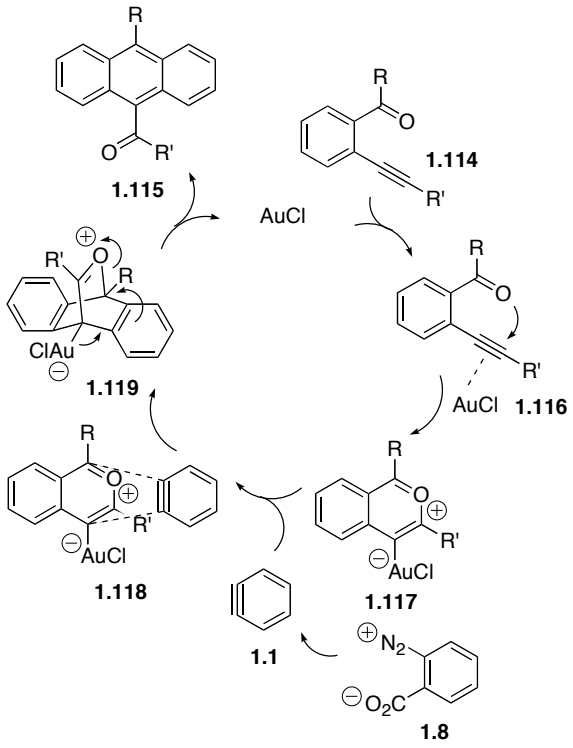
(Eq 1.7)

1.115a: R = PhC≡C, R' = C_3H_7 73%
1.115b: R = *t*-BuC≡C, R' = C_3H_7 73%
1.115c: R = Si(*i*-Pr)$_3$C≡C, R' = C_3H_7 77%
1.115d: R = Ph, R' = Ph 62%

A plausible mechanism for the benzannulation is shown in Scheme 1.12. The reaction proceeds most likely through the [4 + 2] cycloaddition between benzyne and

dipolar diene complex **1.117**. Coordination of alkyne **1.114** to AuCl gives intermediate **1.116**, which undergoes subsequent nucleophilic attack of a carbonyl oxygen to give the dipolar diene **1.117**. The Diels-Alder reaction between diene **1.117** and benzyne **1.1**, derived from **1.8**, generates the bicyclic intermediate **1.119** through **1.118**. The subsequent bond rearrangement, as shown in **1.119** with arrows, releases ring strain, providing stabilized anthracene derivative **1.115** and regenerating AuCl.[33]

Scheme 1.12

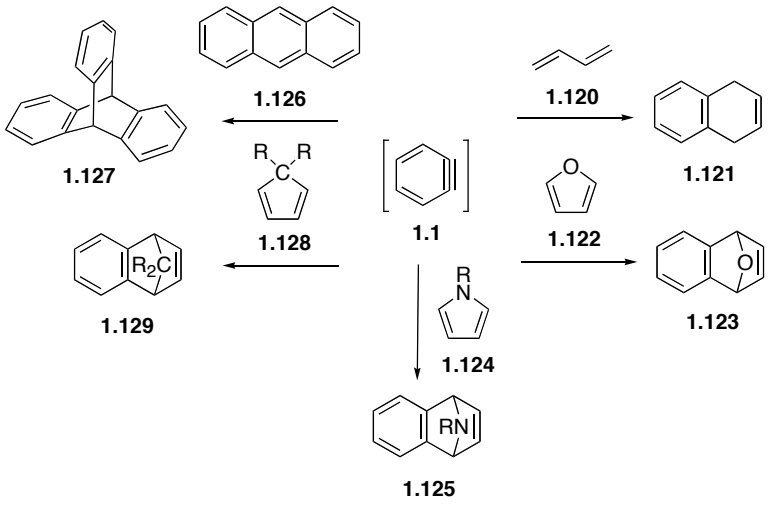


1.4 ARYNE-DIENE CYCLOADDITIONS

The Diels-Alder reaction of arynes with dienes is one of the most important methods in synthetic organic chemistry. Because of the highly electrophilic character of

arynes, the reaction proceeds with a wide range of dienes, including cyclic dienes, acyclic dienes, and aromatic compounds (Scheme 1.13). Intramolecular and intermolecular cycloaddition reactions using aryne intermediates have provided important skeletons of natural products and numerous polyaromatic and polycyclic molecules.[2]

Scheme 1.13



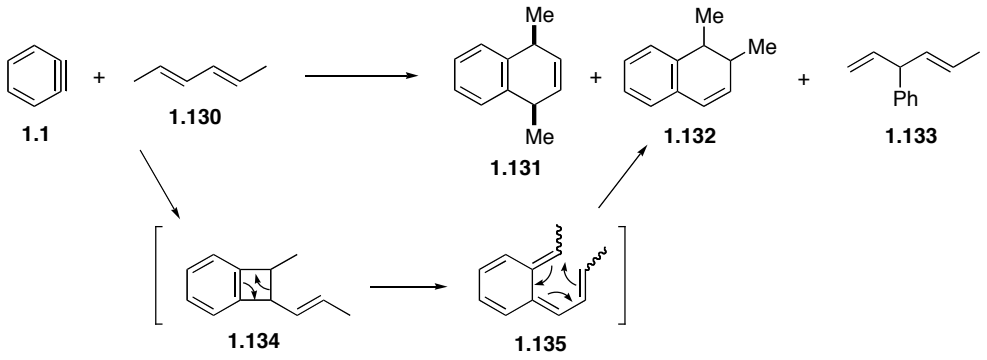
1.4.1 Aryne-Acyclic Diene Cycloadditions

Among the aryne/Diels-Alder reactions, the aryne-cyclic diene cycloaddition is the most common reaction and has been well reviewed.[2] Cycloaddition between an aryne and an acyclic diene was first reported by Wittig in the 1960s.[34] However, there are only few examples of aryne-acyclic diene cylcoaddtions in the literature, and the scope of the reaction has not been investigated in depth.[35]

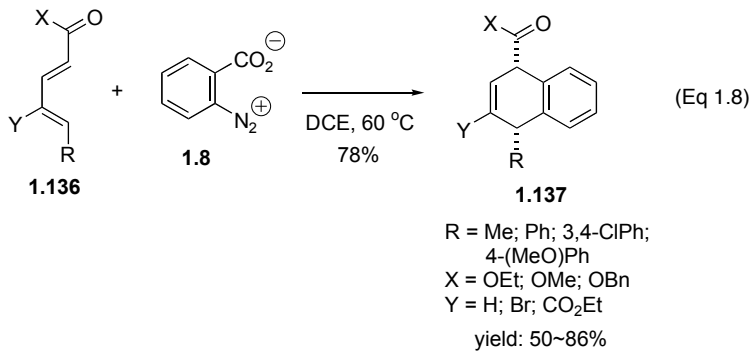
One synthetic application of this type of reaction is the construction of the 1,4-dihydronaphthalene skeleton, which is found in a wide variety of biologically active natural products.[36] A method leading to this skeleton would be highly desirable,

especially if one of the substituents on the diene was a heteroatom or an easily manipulated functional group. Levin found in 1969 that the intermolecular cycloaddition of benzyne with hexadiene (**1.130**) led to the three products **1.131**, **1.132** and **1.133** (Scheme 1.14).[37] The benzyne-diene cycloaddition product, *cis*-1,4-dihydronaphthalene (**1.131**), was produced in 74% yield. Compound **1.132**, which was formed in 4% yield, probably originated from a [2 + 2] addition followed by rearrangement. Compound **1.133**, isolated in 6% yield, was an "ene" reaction product. Therefore, competing reactions among [4 + 2] cycloaddition, [2 + 2] cycloaddition and ene reaction were observed.

Scheme 1.14

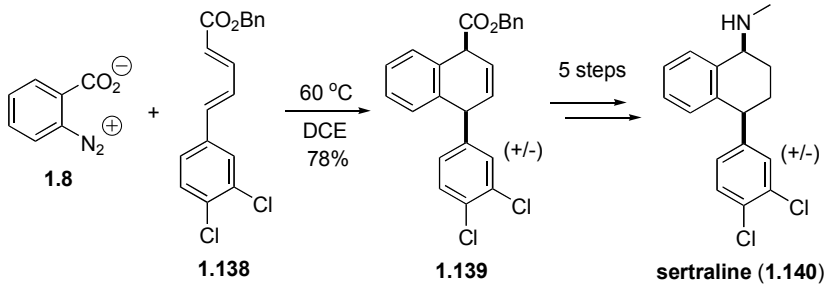


Lautens extended the scope of intermolecular benzyne-acyclic diene cycloaddition in 2005.[38] His method provided a useful approach for the synthesis of highly functionalized 1,4-dihydronaphthalenes **1.137** (Eq 1.8). The *cis* stereochemistry from a concerted [4 + 2] process was obtained. A variety of functional groups on the diene were compatible with the reaction conditions, including esters, halogens and phenyl groups. Reactions with electron-withdrawing substituents on the diene generally proceeded favorably. However, chemoselectivities among [4 + 2] cycloadditions, [2 + 2] cycloadditions and ene reactions were not addressed in the study.

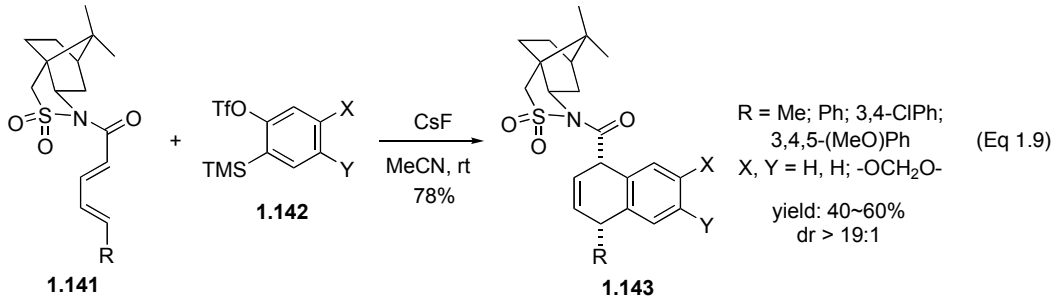


This method was applied to the synthesis of sertraline (**1.140**) (Scheme 1.15).[38] Diels-Alder reaction between benzyne and dienyl ester **1.138** provided dihydronaphthalene **1.139** in good yield. Cycloadduct **1.139** was converted to sertraline **1.140** through hydrogenation, benzyl deprotection, Curtius rearrangement, and methylation.

Scheme 1.15

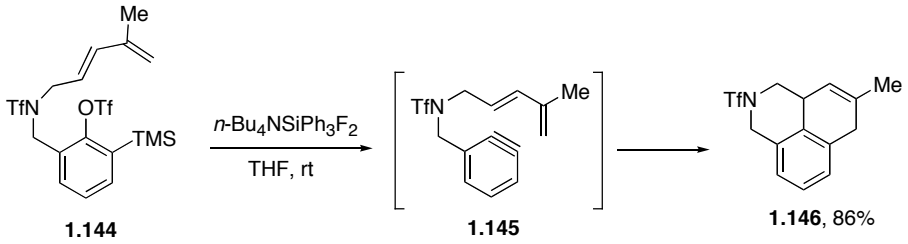


The strategy was further extended to prepare enantiomerically enriched dihydronaphthalenes **1.143** (Eq 1.9). Excellent diastereoselectivities (>19:1) were obtained when Oppolzer's sultam was attached to a diene carbonyl group. Substituted arynes and dienes also participate in the cycloaddition. This is the first report of a diastereoselectivte aryne/Diels-Alder cycloaddition.

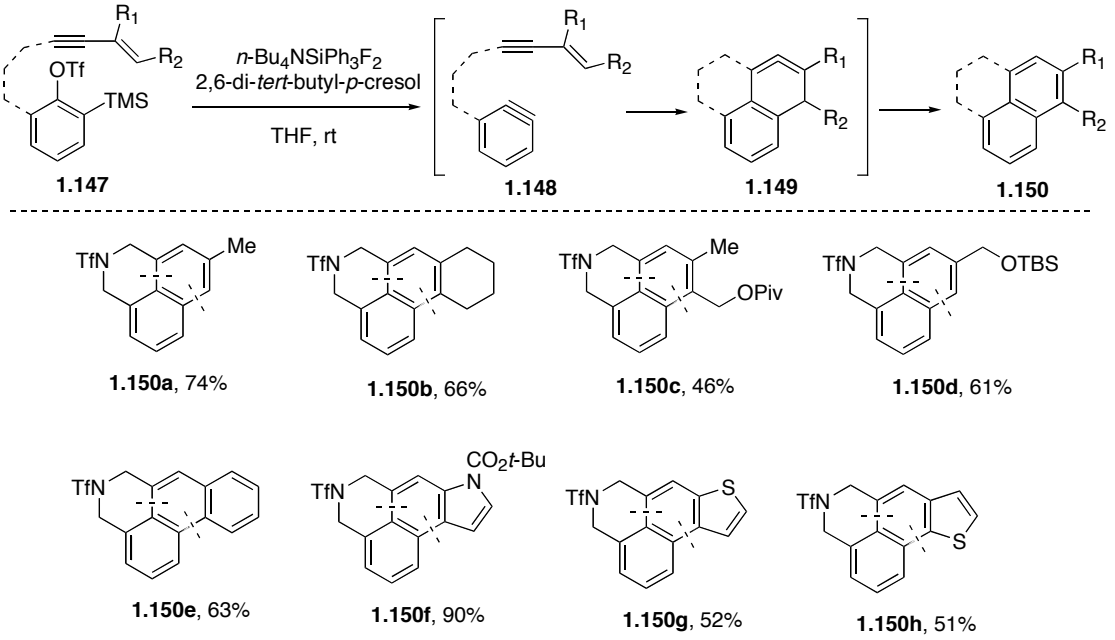


Before 2006, there was only a report regarding the intramolecular Diels-Alder reaction of benzynes with acyclic dienes, although disappointing yields of cycloadducts were obtained.[39] Danheiser reported the first efficient intramolecular cycloaddition of an aryne with acyclic conjugated dienes, enynes and arenynes (Scheme 1.16 and 1.17).[40] This method provides an expeditious route to complex, polycyclic aromatic compounds. This transformation involves the fluoride-induced 1,2-elimination of *o*-trimethylsilylaryl triflates to provide aryne intermediates. Intramolecular cycloaddition with conjugated dienes, enynes and arenynes gives arenes **1.146** and **1.150**. For the formation of **1.150**, the reaction involves the generation of isoaromatic, cyclic, allene intermediates **1.149** (Scheme 1.17). In the presence of 2,6-di-*tert*-butyl-*p*-cresol (BHT), these highly strained intermediates **1.149** then rearrange *via* either proton transfer or radical-mediated hydrogen atom transfer to afford the polycyclic arenes **1.150**.

Scheme 1.16



Scheme 1.17

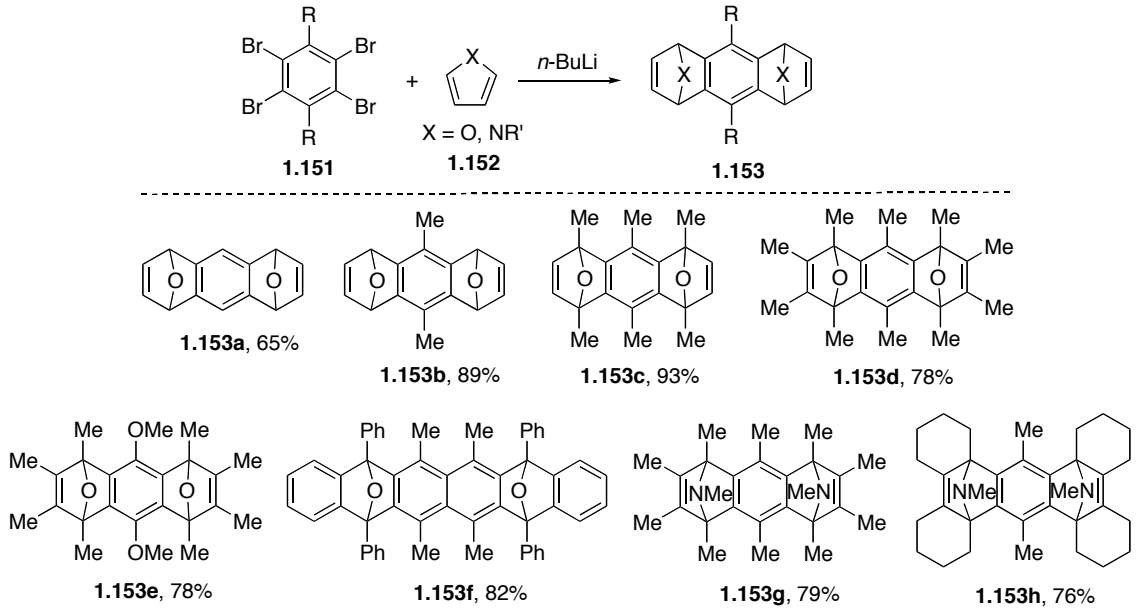


1.4.2 Double Aryne-Diene Cycloadditions

Double aryne-diene cycloadditions were first developed by Hart in 1980,[41] and his method has been extended to the synthesis of supermolecules, materials, and highly strained polycyclic arenes. [42] 1,2,4,5-Tetrabromobenzenes and analogous tetrabromonaphthalenes synthetically function as di-aryne equivalents. These arynes, which can be generated by the metal-halide exchange of tetrabromoarene species with *n*-BuLi and subsequent elimination of the resultant lithium bromide, undergo double cycloadditions with furans, pyrroles and other dienes to give bis-annulated arenes **1.153** (Scheme 1.18). Since aryne intermediates are high-energy species, the cycloadditions are exothermic and, hence, allow for the preparation of a variety of strained compounds. However, the cycloaddition is problematic if the functional groups on the diene or aryne

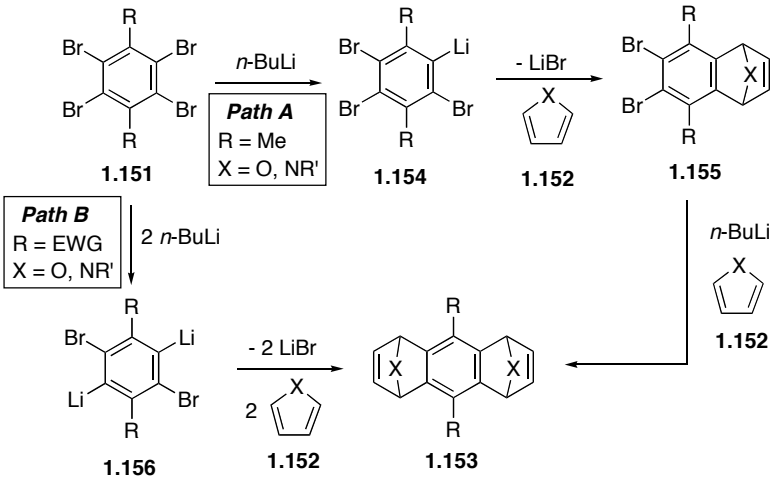
precusor are able to react with *n*-BuLi. Although there are some methods that avoid the use of *n*-BuLi, these methods require more steps for the synthesis of suitable diaryne precursors.[43]

Scheme 1.18



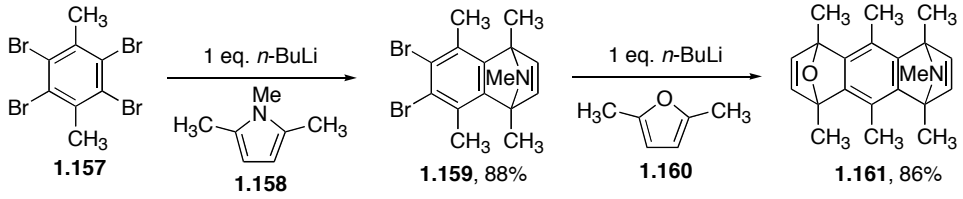
There are at least two possible mechanisms for the double benzyne-diene cycloaddition (Scheme 1.19),[44] with the main difference being how the aryl lithium intermediate is generated. Treatment of **1.151** with an organolithium reagent gives either a monolithio derivative **1.154** (path A) or a dilithio derivative **1.156** (or its 1,3-isomer; path B). Both paths lead to the same product **1.153**. These paths are distinguishable by isolation of products or performing deuterium-label experiments. Hart has shown that when R is methyl group, path A is followed, but the reaction proceeds *via* path B when R is an electron-withdrawing substituent, such as a chlorine atom.

Scheme 1.19



Treatment of a mixture of *p*-tetrabromoxylene **1.157** and pyrrole **1.158** with one equivalent of *n*-BuLi at -78 ºC provided monoadduct **1.159** in 88% yield (Scheme 1.20). Monoadduct **1.159** was submitted for another cycloaddition with furan **1.160** to give biscycloadduct **1.161**. This result is consistent with path A.

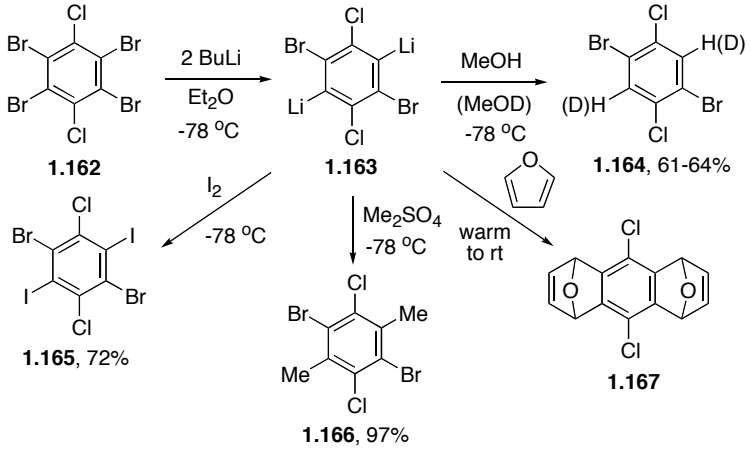
Scheme 1.20



In another experiment, 2.2 equivalents of *n*-BuLi were added to a mixture of *p*-dichlorotetrabromobenzene **1.162** in the presence of a large excess of furan at -78 ºC (Scheme 1.21). The reaction was quenched with methanol at the same temperature to provide 1,4-dibromo-2,5-dichlorobenzene **1.164** as a single product.[44] If the reaction was quenched with deuterated methanol-d_4, dideuteroarene **1.164** was obtained. But if the reaction mixture was warmed to room temperature for 6 h before quenching with

deuterated methanol-d_4, the product was the bis-adduct **1.167**. These results indicated that metal-halogen exchange occurred at -78 °C preferentially with the bromine substituents to give exclusively the *para-dilithio* intermediate **1.163**. Elimination of the lithium bromide to give the aryne followed by cycloaddition with diene occurred when warmed to room temperature. At -78 °C, the dilithio intermediate **1.163** can be trapped with iodine and dimethylsulfate to furnish **1.165** and **1.166**, respectively. These results indicate that the reaction proceeds path B.

Scheme 1.21

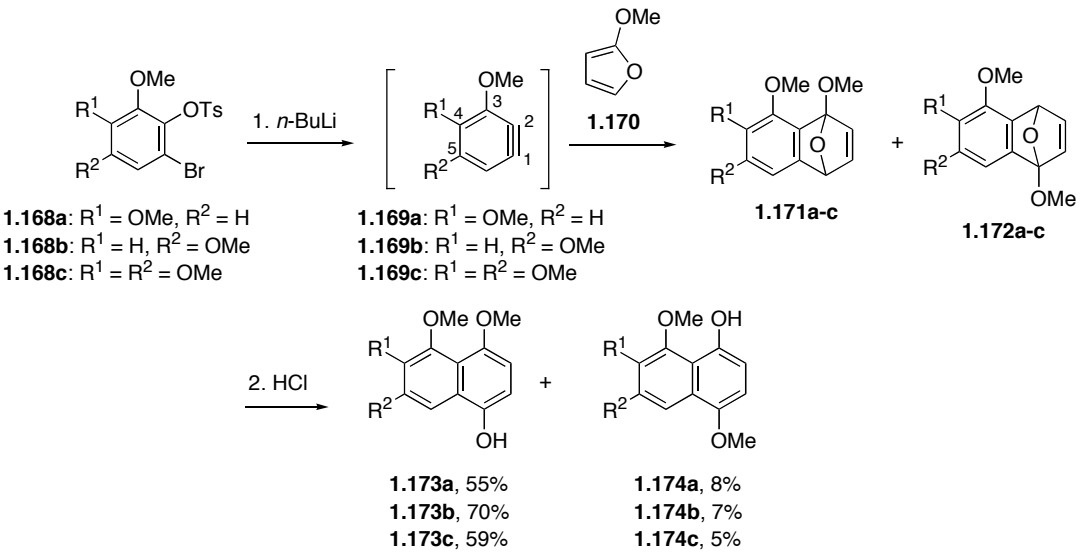


1.4.3 Regioselectivity of Aryne-Cyclic Diene Cycloadditions

The cycloaddition of a 3-alkoxybenzyne with a 2-alkoxyfuran is highly regioselective.[5] Sargent reported that cycloaddition of 3,4-dimethoxybenzyne **1.169a**, derived from *o*-elimination of substituted bromoanisole **1.168a** with *n*-BuLi, with 2-methoxylfuran provided cycloadducts **1.171a** and **1.172a**. The cycloaddition was followed by acid-catalyzed ring opening to give predominantly naphthol **1.173a** together with **1.174a**, a minor isomer (Scheme 1.22).[45] Good regioselectivities were also obtained

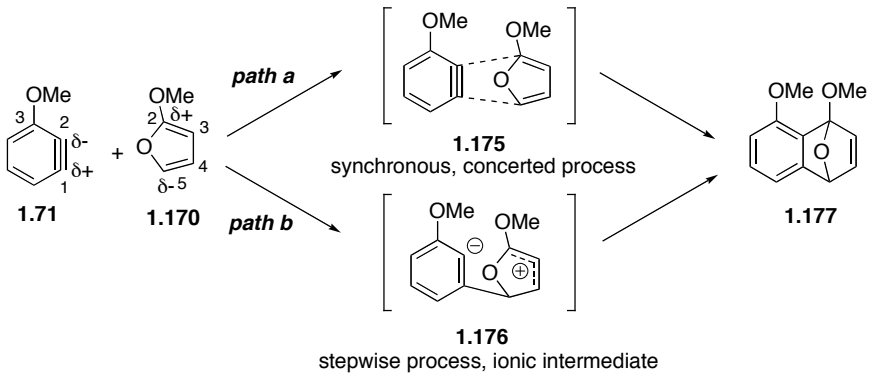
when the substituted 3-methoxybenzyne precusors **1.168b**-**c** were used.

Scheme 1.22



Sargent proposed two possible mechanisms for these [4 + 2] cycloadditon reactions.[45] The first is a synchronous, concerted process in which two new bonds are formed to some extent in the transition state (Scheme 1.23, path a). For this process, the electronic effect presumably dominates the steric effect. The good regioselectivities are attributed to the inductive effect induced in the benzyne by the C3 methoxy group coupled with electron-releasing property of the 2-methoxy group in the furan.[45,5] Inductive effect enhances the electrophilicity of the C1 position in a benzyne **1.71**, whereas C5 position of furan **1.170** has more partial negative charge character due to the electron-releasing property of 2-methoxy group. Thus, during cycloaddition process the C1 position of benzyne directs the C5 position of furan and, thus, these cycloadditions provide good regioselectivities.

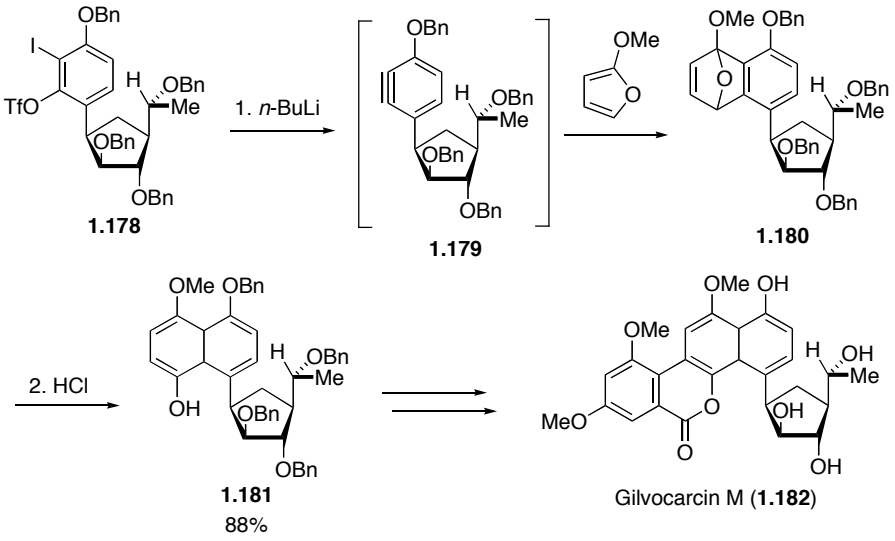
Scheme 1.23



The second mechanism is a stepwise process in which an ionic intermediate is involved (Scheme 1.23, path b). For this process, inductive effect directs carbon-carbon bond formation between C1 of benzyne and C5 of furan. In addition, steric effect rendered the addition of a furan at C1 position of benzyne since C1 position is less hindered than C2 position. The developing negative charge in **1.176** can be inductively stabilized to a greater extent due to C3 methoxy group on the aromatic ring.

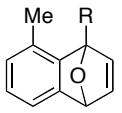
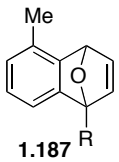
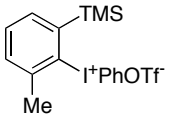
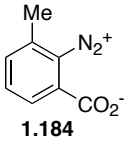
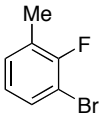
Based upon these advances, Suzuki applied the regioselective cycloadditions of benzyens and furans to the total synthesis of (–)-gilvocarcin M (**1.182**).[46] Treatment of *o*-iodoaryl triflate **1.178** with *n*-BuLi in THF at -78 ºC in the presence of 2-methoxyfuran resulted in the benzyne formation and subsequent [4 + 2] cycloaddition to give cycloadduct **1.180** (Scheme 1.24). The regioselectivity of cycloaddition was directed by 3-benzyloxybenzyne **1.179** and 2-methoxyfuran. Aromatization of **1.180** with hydrochloric acid provided naphthol **1.181** in 88% yield together with 7% of the regioisomers. Coupling of naphthol **1.181** with 3,5-dimethoxy-2-iodobenzoic acid followed by Pd-catalyzed cyclization and deprotection of the benzyl groups furnished (–)-gilvocarcin M (**1.182**).

Scheme 1.24

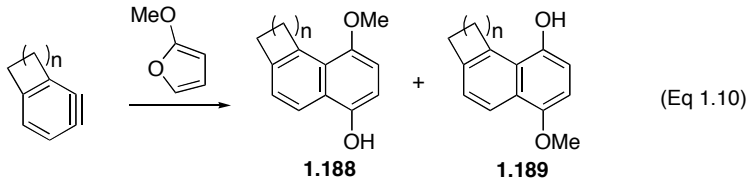


Regioselectivity is poor, however, for the Diels-Alder reaction of 3-alkyl benzynes with 2-alkylfurans.[47] The ratios of the cycloadducts obtained in the reaction of 3-methylbenzyne, derived from three different benzyne precursors **1.183**-**1.185**, with 2-alkyl furans (2-methyl furan and 2-*tert*-butyl furan) are summarized in Table 1.1.[47] These results show that the reaction only slightly prefers the cycloadducts **1.187**. For a concerted cycloaddition process, the inductive effect for 3-alkyl benzyne is not obvious since these alkyl groups are not good electron-donating groups. Steric repulsion between substituted groups on benzyne and furan would lead to the products **1.187**. For a stepwise process, C2 position of benzyne possesses part of electrophilic character. It would direct addition of C5 position of furan bearing slight negative charge character to provide more ratios of products **1.187**. These three benzyne precursors provide similar ratios of **1.186** to **1.187**, which indicates that the nature of the benzyne generated from the hypervalent iodine-benzyne precursor **1.183** is similar to that from benzenediazonium-2-carboxylate **1.184** and 1,2-dihalobenzenes **1.185**. In addition, regioselectivities are also very similar for both 2-methyfuran and 2-*tert*-butylfuran.

Table 1.1 The Ratio of Cycloadducts in Benzyne-Furan Cycloadditions

3-Methylbenzyne Precursor	2-substituted furan	Yield(%)	Yield and Ratio of Adducts:  **1.186**	Yield and Ratio of Adducts:  **1.187**
 **1.183**	Me	100	33	67
	tert-Bu	72	30	70
 **1.184**	Me	50	42	58
	tert-Bu	51	34	66
 **1.185**	Me	74	42	58
	tert-Bu	73	36	64

Another regioselective [4 + 2] cycloaddition is observed in a benzyne that contains a fused four-membered ring.[5] Inductive effect, induced by a fused four-membered ring, renders C1 position of benzyne more electrophilic (see discussion for Figure 1.4) and directs the cycloaddition with 2-methoxyfuran. For example, cycloaddition of benzyne **1.36a** with 2-methoxyfuran followed by aromatization with hydrochloric acid gives phenol **1.188a** as the major product (4.0:1) in 58% yield (Eq 1.10). However, inductive effect is not clear for benzynes **1.36b** and **1.36c** that contain larger fused ring systems. Therefore, cycloaddition of benzyne **1.36b**-**c** with 2-methoxyfuran provides poor or opposite regioselectivities.

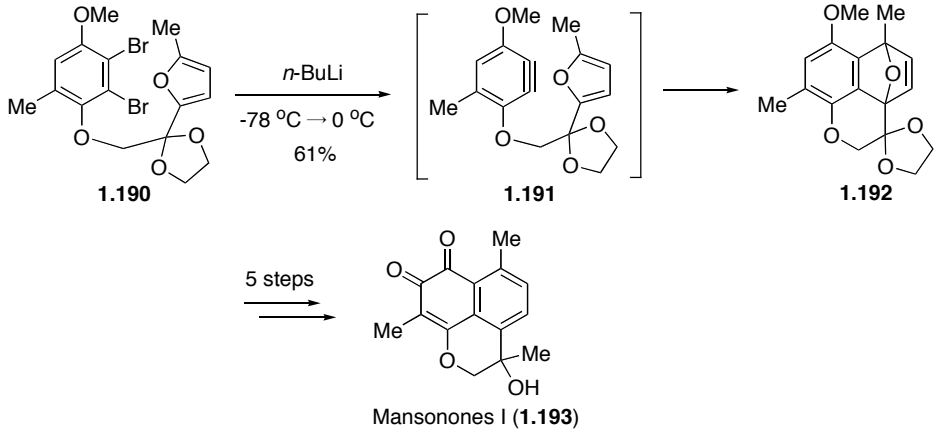


1.188 **1.189**

1.36a: n = 1 n = 1, 72%, **1.188a/1.189a** = 4.0:1
1.36b: n = 2 n = 2, 79%, **1.188b/1.189b** = 1.4:1
1.36c: n = 3 n = 3, 50%, **1.188c/1.189c** = 1:1.4

The inductive effect derived from benzyne and furan substrates plays an important role in regioselective benzyne-furan cycloadditions. In order to extend the regioselective cycloadditions to more general benzyne and furan substrates, Wage developed intramolecular Diels-Alder cycloaddtions of furans with tethered benzynes, and demonstrated the method for the total synthesis of natural products.[48] These benzynes, which were generated by the debromination of an *o*-dibromobenzene **1.190**, or by the thermolysis of a substituted diazotized anthranilic acid **1.194**, underwent cycloadditions with attached furan moieties. The resultant cycloadducts **1.192** and **1.196** served as the key intermediates for the synthesis of mansonones I (**1.193**), F (**1.197**), E (**1.198**), and biflorin (**1.199**).

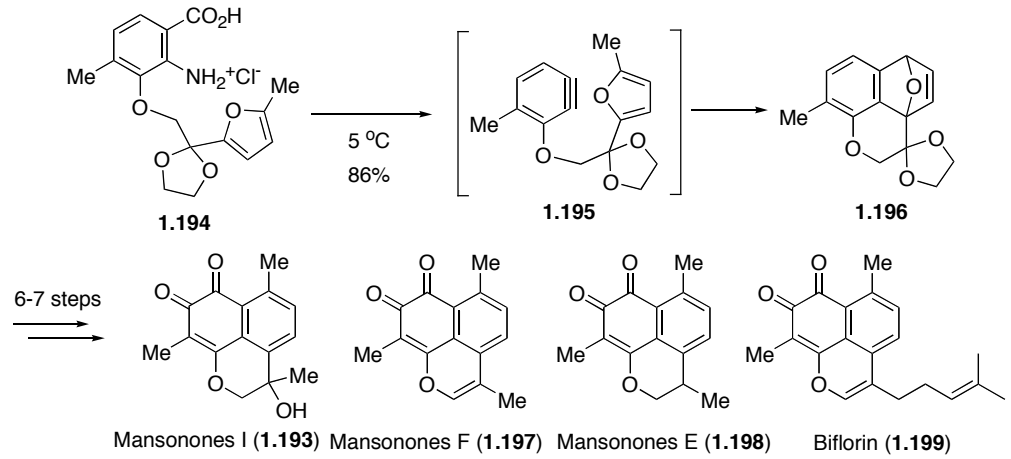
Scheme 1.25



1.190 **1.191** **1.192**

Mansonones I (**1.193**)

Scheme 1.26



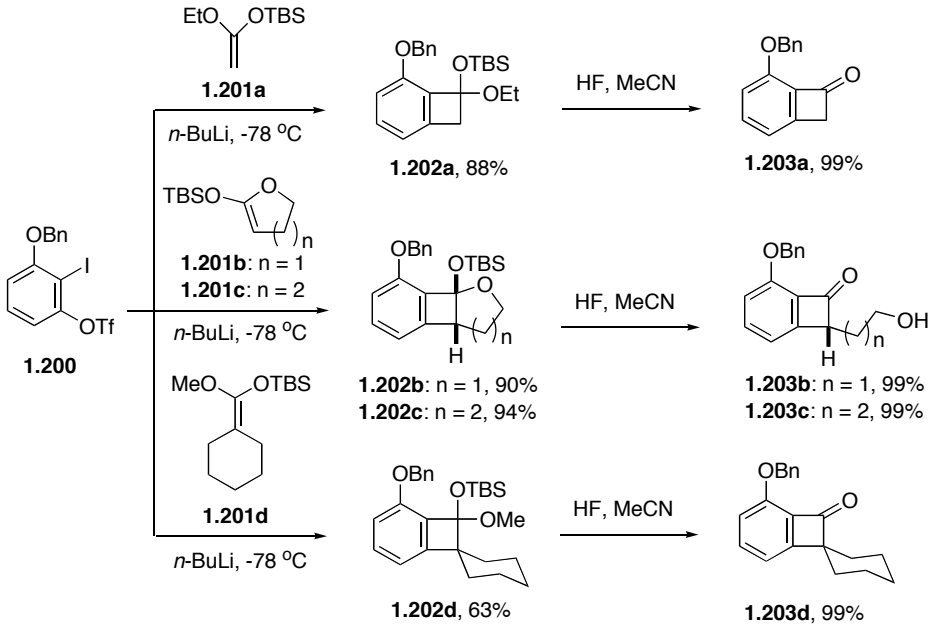
1.5 [2+2] CYCLOADDITIONS WITH ARYNES

Aryne-alkene [2 + 2] cycloadditions are thermally allowed due to the unusually low-lying LUMO of arynes. The [2 + 2] cycloaddition of arynes with alkenes certainly provides the most direct route to benzocyclobutenes, which have been recognized as valuable intermediates in organic synthesis.[2,49] These reactions usually proceed best with alkenes bearing electron-donating substituents or with simple alkenes.[50] Although a number of these cycloadditions are documented, the scope of the reaction is limited, primarily due to the drastic conditions that are conventionally employed for generating benzynes.[2]

Suzuki recently reported a mild and efficient regioselective [2 + 2] cycloaddition. Treatment of *o*-iodoaryl trifalte **1.200** with *n*-BuLi in the presence of silyl ketene acetals **1.201a**-**d** provided cyclobutanes **1.202a**-**d** in good yields with high regioselectivities (Scheme 1.27).[51] It is worth noting that the sterically hindered trisubstituted and tetrasubstituted silyl ketene acetals **1.201b**-**d** serve as good partners for these [2 + 2]

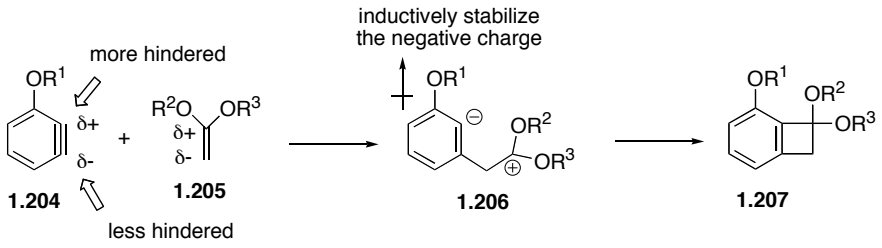
cycloadditions. Subsequent acid-catalyzed hydrolysis of cyclobutanes **1.202a**-**d** gave ketones **1.203a**-**d**.

Scheme 1.27

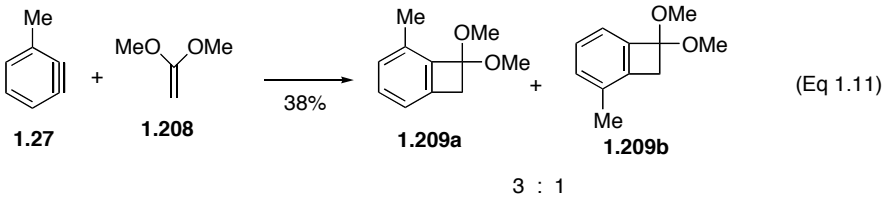


Both Stevens and Kessar claimed that [2 + 2] cycloaddition presumably proceeds *via* a stepwise process since suprafacial/antarafacial orbital overlap is allowed (Scheme 1.28),[2b,52] but experimental precedent is lacking. The high regioselectivity of the [2 + 2] cycloadditions can be attributed to the inductive effect of the C3 alkoxy group on benzyne **1.204**, which directs attack of the β-carbon of silyl ketene acetal **1.205** to the most electron-deficient carbon of the benzyne triple bond. Other reasons, such as inductive stabilization of an ionic intermediate **1.206** by C3 alkoxy group, and steric effect, also enhance regioselectivities.

Scheme 1.28

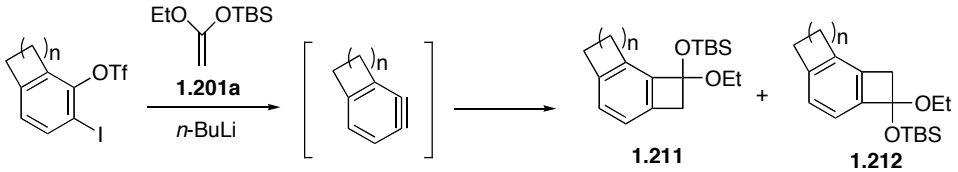


For 3-methylbenzyne, inductive effect derived from methyl group is weak, and the preferred orientation relies on the steric effect to align the approaching mucleophile (Eq 1.11). Therefore, a head-to-head preference is observed.



Another regioselective [2 + 2] cycloaddition was observed with benzyne **1.36a**, possessing a fused four-membered ring.[5] The good regioselectivity was attributed to inductive effect induced by a fused four-membered ring (see discussion for Figure 1.4 and Eq 1.10). Upon treatment of *o*-iodoaryl trifate **1.210a** with *n*-BuLi in the presence of silyl ketene acetal **1.201a**, the [2 + 2] cycloaddition ensued to give cycloadduct **1.211a** preferentially (Scheme 1.29). However, the regioselectivity dramatically decreased for reactions involving benzynes **1.36b**-**c** possessing larger fused rings, giving a regioisomeric mixture of cycloadducts.

Scheme 1.29



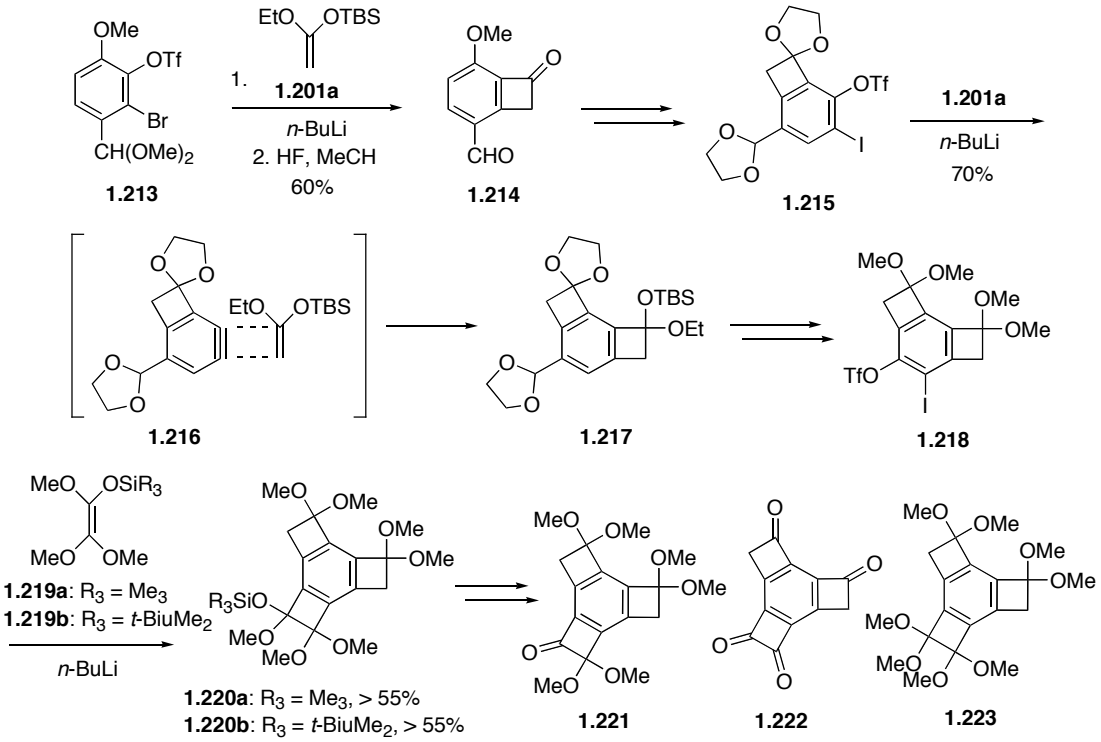
1.210a: n = 1
1.210b: n = 2
1.210c: n = 3

1.36a: n = 1
1.36b: n = 2
1.36c: n = 3

n = 1, **1.211a/1.212a** = 22:1
n = 2, **1.211b/1.212b** = 2.3:1
n = 3, **1.211c/1.212c** = 5.7:1

The regioselective [2 + 2] cycloadditions of benzynes with silyl ketene acetals were applied to the synthesis of tricyclobutabenzenes **1.221**-**1.223** (Scheme 1.30).[53] Treatment of bromotriflate **1.213** with *n*-BuLi in the presence of silyl ketene acetal **1.201a** followed by acid-catalyzed hydrolysis cleanly gave ketoaldehyde **1.214** as a single product. Ketoaldehyde **1.214** was converted into acetal **1.215** in four steps. Next, the second cylcoaddition of benzyne **1.216**, derived from **1.215**, with silyl ketene acetal **1.201a** gave cycloadduct **1.217** as a single isomeric product, and this was converted into *o*-iodotriflate **1.218** in six manipulations. The third cycloaddition of *o*-iodotriflate **1.218** with silyl ketene acetals **1.219a**-**b** provided cycloadducts **1.220a**-**b**. These two cycloadducts were selectively transformed to tricyclobutabenezenes **1.221**-**1.223**. The repeated regioselective [2 + 2] cycloadditions have enabled a general approach to various structurally elaborate tricyclobutabenzenes with oxygen functionalities.

Scheme 1.30

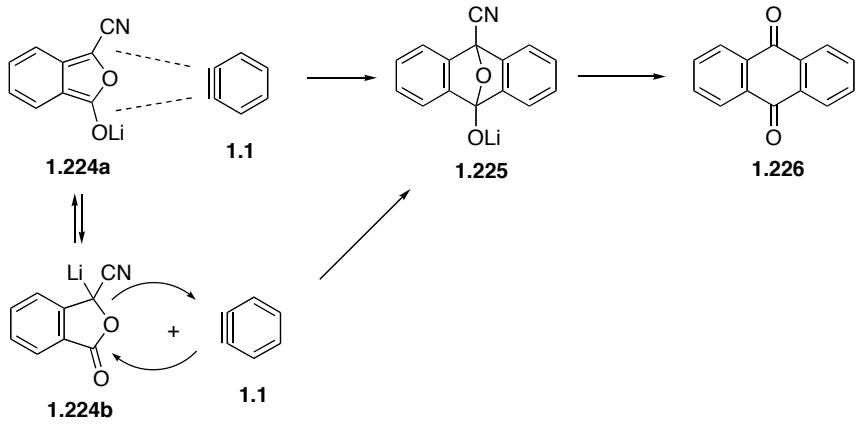


1.6 1,4-DIPOLAR CYCLOADDITIONS WITH ARYNES

1,4-Dipolar cycloadditions with arynes have been applied to the synthesis of anthraquinone derivatives and natural products, although there are few examples in the literature.[2] In 1987, Biehl reported the first example of a 1,4-dipolar cycloaddition with arynes.[54] His method allowed for an efficient combination of two aryl groups to give an anthraquinone skeleton in a single step, providing a new entry to a daunomycinone intermediate, islandicin, digitopurpone, pachybasin, chrysophanol, ziganein and helminthosporin.[54,55,56] The key step involved cycloaddition of aryne **1.1** with the phthalide anion **1.224a** and subsequent rearrangement to give anthraquinone **1.226** (Scheme 1.31). Although both Biehl and Wege showed that the mechanism was a

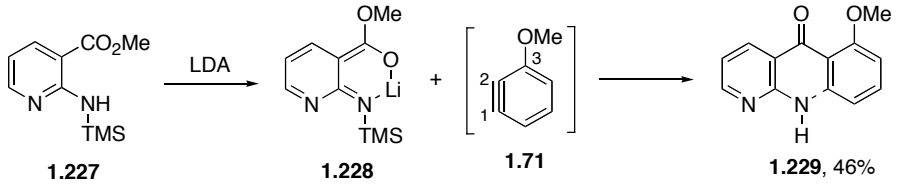
concerted process,[57] it could not be excluded that nucleophilic attack of carbanion **1.224b** on aryne **1.1** followed by addition of the resultant aryl lithium to the ester gave intermediate **1.225**.

Scheme 1.31



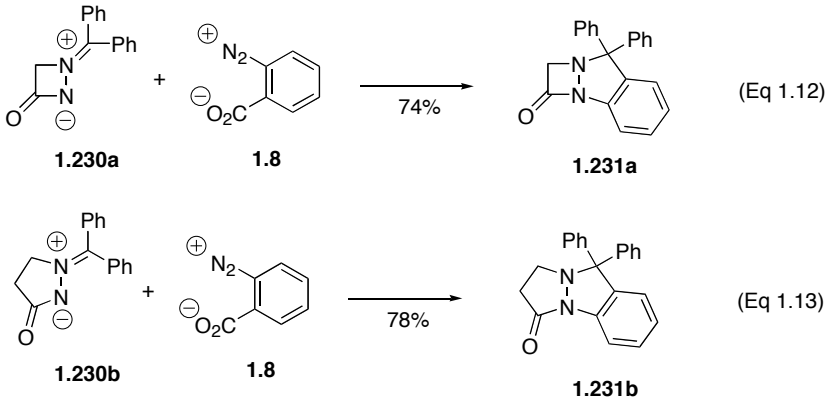
This approach was extended to the synthesis of azaacridones **1.229** (Scheme 1.32). [58] For example, cycloaddition of *N*-lithiated anthranilate **1.228** with 3-methoxybenzyne **1.71** provided azaacridone **1.229** as the exclusive product in 46% yield. The good regioselectivity of the cylcoaddition was attributed to the strong electron-withdrawing group at the C3 position of **1.71**, which directed addition of *N*-lithiated anthranilate **1.228**.

Scheme 1.32



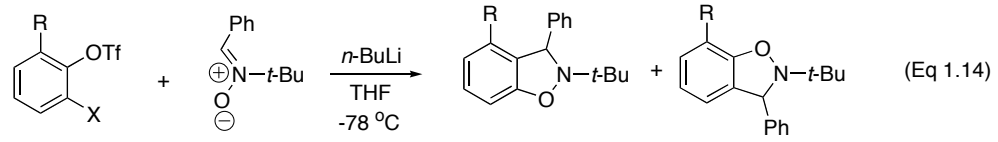
1.7 1,3-DIPOLAR CYCLOADDITIONS WITH ARYNES

1,3-Dipolar cycloadditions with arynes have been investigated over the past few decades.[2] A wide variety of stable 1,3-dipolar compounds underwent cycloaddition with arynes to give five-membered ring products. For example, Taylor reported that the salts of 3-oxo-1,2-diazetidinium hydroxides **1.230a**-**b** reacted with benzynes, which was generated from benzenediazonium carboxylate (**1.8**), in THF to give the bicyclic adducts **1.231a**-**b** in good yields (Eq 1.12 and Eq 1.13).[59] A variety of bicyclic derivatives have been synthesized by this method, and yields depend on the substituents present.



Suzuki reported a detailed study of C3 substituted aryne-nitrone cycloadditions. [60] Suzuki rationalized that the 1,3-dipolar cylcoaddition is a stepwise process, and regioselectivities are influence by both inductive and steric effect. In his experiments, *n*-BuLi was added to a solution of *o*-halotriflate **1.232a** and nitrone **1.233** in THF at -78 °C, where the generation and cycloaddition of the aryne occurred (Eq 1.14). The reaction proceeded almost instantaneously to deliver the adduct **1.234a** in 91% yield. The high regioselectivity was presumably due to the C3 electron-withdrawing alkoxy group of the benzyne. The attack of an oxygen atom occurred preferentially at the least hindered and

most electron-deficient carbon atom of benzyne to give a more stable aryl anion intermediate (see discussion in Chapter 1.2.1).



(Eq 1.14)

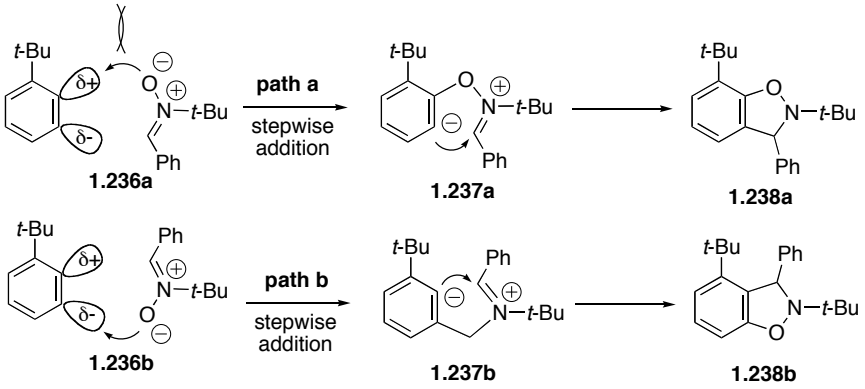
1.232a: X = I, R = OMOM **1.233**
1.232b: X = Br,R = TMS
1.232c: X = Br,R = TBS
1.232d: X = Br,R = Me
1.232e: X = Br,R = *t*-Bu

1.234a: 91% **1.235a**: 0%
1.234b: 5% **1.235b**: 89%
1.234c: 12% **1.235c**: 82%
1.234d: 23% **1.235d**: 63%
1.234e: 76% **1.235e**: 14%

Trialkylsilyl substituents are expected to be electron-donating groups, which may enhance the electrophilicity at C2 of benzyne relative to C1 and prefer addition of an oxygen atom at C2 position of benzyne. Steric hindrance of silyl groups is not an important issue since C-Si bond is longer than C-C bond. Therefore, 1,3-dipolar cycloadditions with **1.232b**-**c** gives adducts **1.235b**-**c** preferentially. The cycloaddition of 3-methylbenzyne with **1.233** provided **1.235d** as the major isomer. The regioselectivity was modest (**1.234d** : **1.235d** = 1 : 2.8) presumably, due to the weak inductive effect induced by C3 methyl group and steric effect of a C3 methyl group on the benzyne.

The cycloaddition of 3-*tert*-butylbenzyne with **1.233** provided opposite regiochemical outcomes.[61,62,63] The inductive effect from *tert*-butyl group is weak, but the steric effect is obvious. Compare the two paths in Scheme 1.33, the C-O bond formation *via* path b is presumably favorable, since the oxygen attack is less sterically encumbered. Thus, path b dominates the reaction.

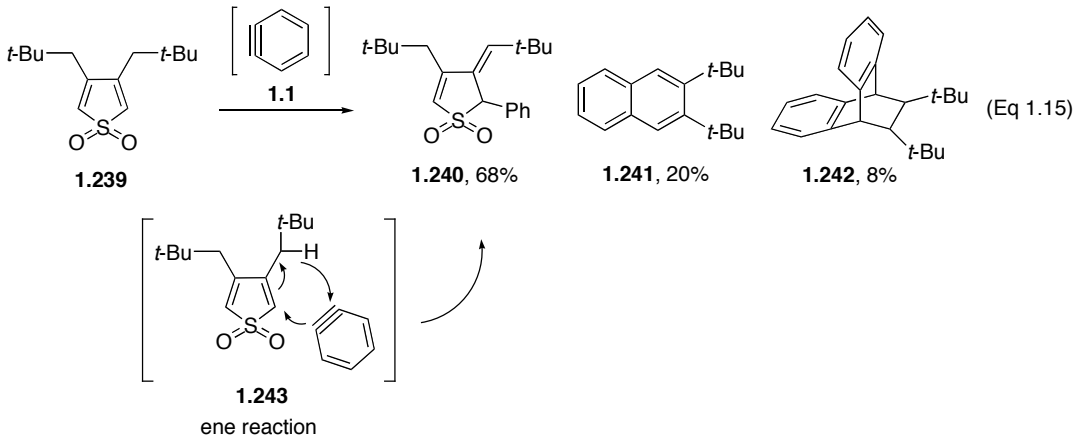
Scheme 1.33



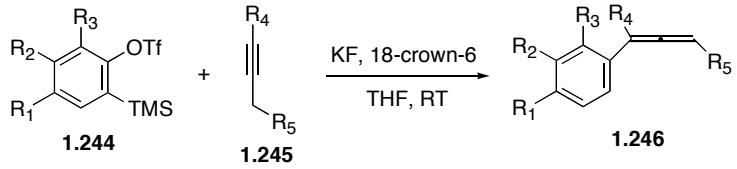
1.8 ENE REACTIONS WITH ARYNES

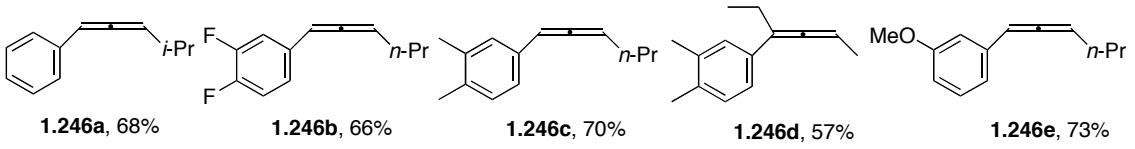
Although arynes are good electrophilic partners in [4 + 2], [2 + 2] and dipolar cycloadditions, they are not good enophiles in ene reactions,[2] and there are few reports of aryne ene reactions.[2] Among of them, efficient ene reactions are very limited and most are observed as side reactions in [4 + 2] or [2 + 2] cycloadditions. A related example is described in Scheme 1.14.[37]

It was recently reported that thiophene dioxide **1.239** underwent efficient Diels-Alder reactions with a variety of dienophiles, such as phenyl vinyl sulfone, dimethyl acetylenedicarboxylate and cyclooctyne.[64] However, the cycloaddition of **1.239** with benzyne provided mainly ene reaction adduct **1.240** together with small amount of the expected Diels-Alder product **1.241** and barrelene **1.242**, which was derived from further cycloaddition of **1.241** with benzyne (Eq 1.15).

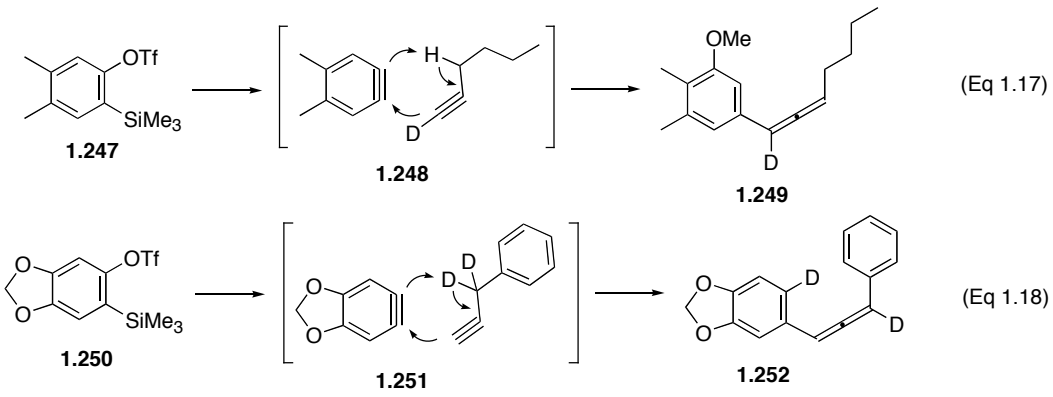


Cheng recently reported an efficient aryne ene reaction, wherein arynes, generated from the reaction of *ortho*-silylaryl triflates **1.244** with KF/18-crown-6, underwent ene reactions with alkynes **1.245** to give substituted phenylallenes **1.246** (Eq 1.16).[65] Several terminal and internal alkynes possessing propargylic hydrogens were effective reaction partners to deliver the corresponding phenylallenes in good to moderate yields. When 3-methoxybenzyne was used, the *meta* isomer **1.246e** was obtained as the exclusive product. This is the only example of regioselective ene reaction with asymmetric aryne.





In order to elucidate the mechanism of the reaction, two deuterated substrates were submitted to the ene reaction condition to provided allene products **1.249** and **1.252**, respectively (Eq 1.17 and Eq 1.18). These results indicated that ene reaction proceeded *via* orientation **1.248** and **1.251** to provide deuterated products.



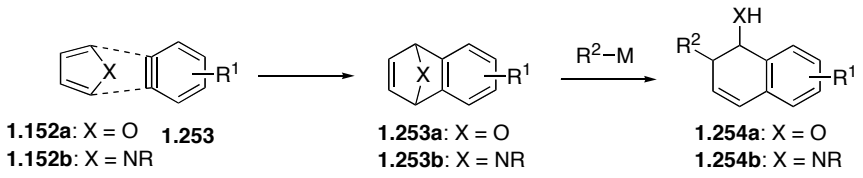
1.9 APPLICATION OF BENZYNE-DIENE CYCLOADDITION ADDUCTS IN ORGANIC SYNTHESIS

1.9.1 Transition Metal-Catalyzed Ring Opening of Oxabenzonorbornadienes and Azabenzonorbornadienes

1.9.1.A Overview

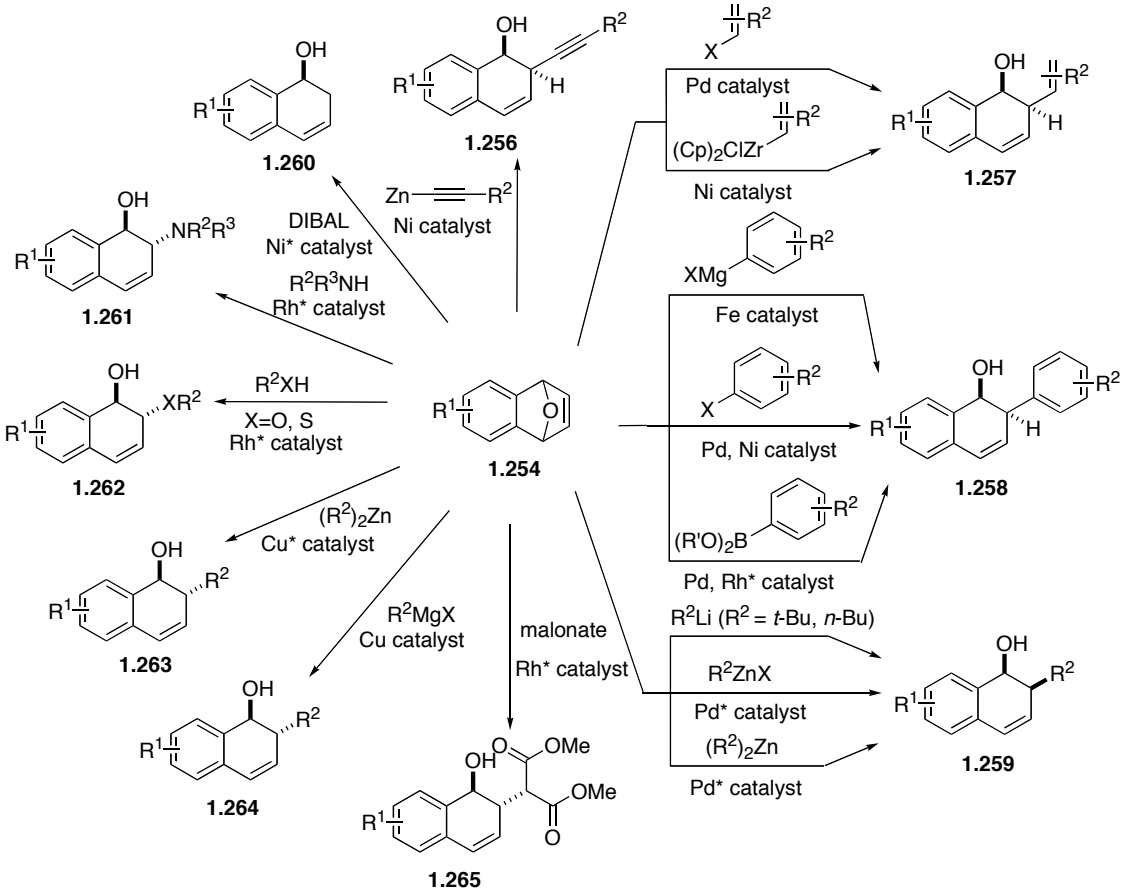
The Diels-Alder cycloadditions of benzynes with furans readily provide oxabenzonorbornadienes **1.253a** (Scheme 1.34). These cycloadducts have been extensively employed in the ring opening reaction in the presence of transition metal catalyst to generate functionalized *cis*- and *trans*-2-substituted-1,2-dihydronaphthols **1.254**.[66] The ring opening strategy has extended to azabenzonorbornadiene derivatives **1.253b**. The application of these methodologies has found use in the total synthesis of several natural products and biologically active molecules.[66]

Scheme 1.34



These reactions may be carried out with a range of nucleophiles, including stabilized and nonstabilized carbanions,[67,68,69,70,71,72,73,74,75] hydride,[76] sulfides,[77] alcohols,[78] and amines,[78] thereby allowing installation of new functionalities on the oxabicyclic frameworks (Scheme 1.35). These ring opening reactions require transition metal catalysts, and several transition metals can be employed, including nickel, palladium, iron, copper, and rhodium. It is worth noting that butyllithiums are nucleophilic enough to open oxabenzonorbornadienes in the absence of transition metal catalysts.[72] Enantioselective ring opening reactions are accomplished with a variety of metal catalysts bearing chiral ligands. Since there are numerous ring opening strategies reported, this Chapter will only introduce some interesting examples and methodologies relevant to our research in Chapter 2.

Scheme 1.35



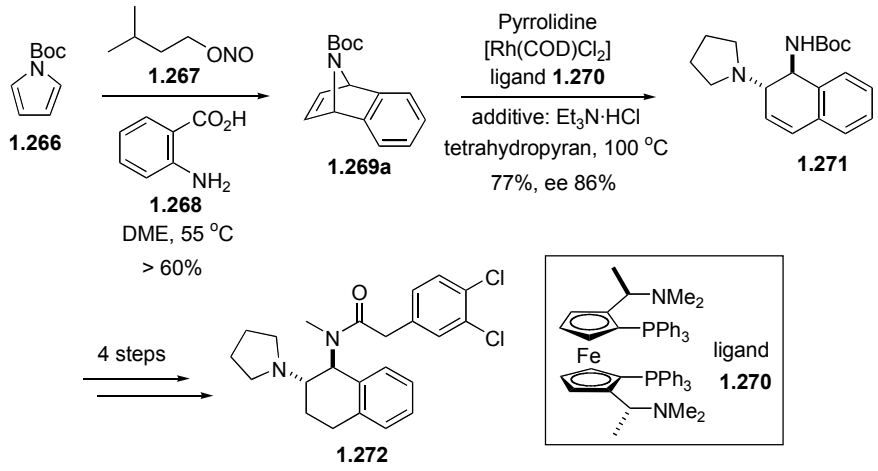
* chiral catalyst for enantioselective ring opening reaction

1.9.1.B Using Amines for Ring Opening Reactions

Lautens reported the rhodium-catalyzed enantioselective ring opening of azabenzonorbornadienes with amines to provide diaminotetralins.[79] The methodology was applied to prepare the 1,2-diamino motif **1.272**, which was reported to be a highly selective κ-opioid agonists.[80] Enantioselective ring opening of azabenzonorbornadiene **1.269a**, which was produced from benzyne and pyrrole **1.266**, with pyrrolidine proceeded smoothly in the presence of $[Rh(COD)Cl]_2$, ferriphos **1.270**, $Et_3N{\cdot}HCl$ and

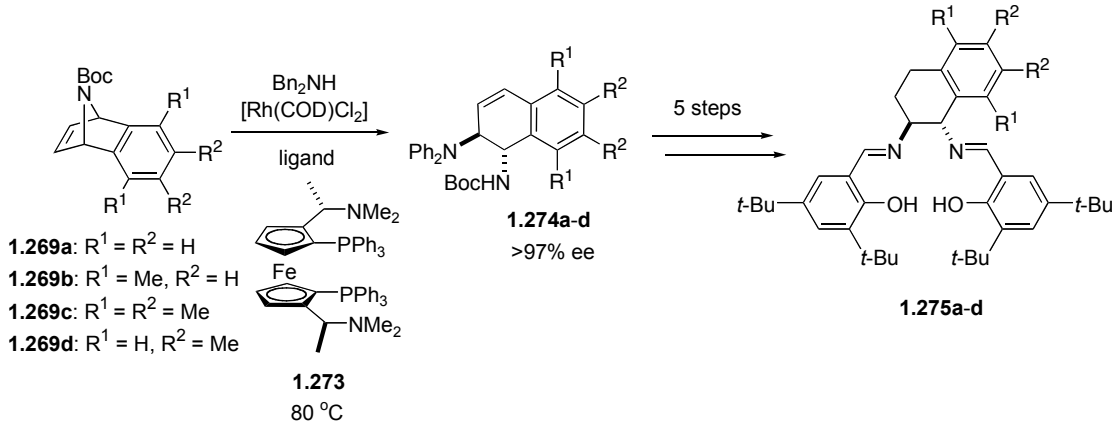
tetrahydropyran to produce **1.271** (Scheme 1.36). Methylation of **1.271** followed by removal of the Boc group and coupling with arylacetic acid furnished enantiomerically enriched 1,2-diamino **1.272**.

Scheme 1.36



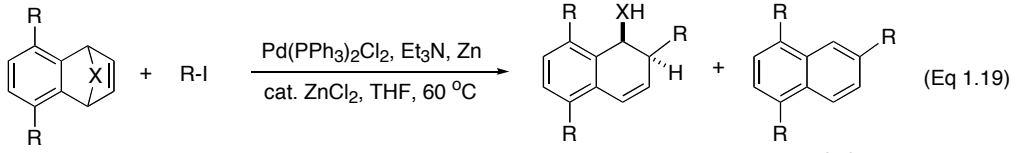
Rhodium-catalyzed ring opening of azabenzonorbornadienes **1.269a**-**d** with dibenzylamine provided good yield of the corresponding products **1.274a**-**d** with greater than 97% ee (Scheme 1.37).[81] The optically active ring-opened products **1.274a**–**d** thus obtained were easily converted into Jacobsen-type salen ligands **1.275a**–**d** in five steps.

Scheme 1.37



1.9.1.B Using Aryl and Vinyl Halides for Ring Opening Reactions

Most relevant to our research in Chapter 2 are the methodologies developed by Cheng. He has developed palladium-catalyzed stereoselective ring openings of oxabenzonorbornadienes and azabenzonorbornadienes with aryl and vinyl halides to give the corresponding racemic *cis*-2-substituted-1,2-dihydro-1-naphthalenes **1.277** (Eq 1.19).[67a-b] Although the metal-catalyzed ring opening of bicyclic alkenes with a variety of triflate, zinc, Grignard, and boronic acid reagents can provide similar products (see Scheme 1.35), the use of commercially available aryl and vinyl halides for the reaction is more convenient. Cheng found that couplings with a wide range of electron-rich aryl and vinyl iodides provided good yields of products **1.277**. However, reactions involving electron-deficient aryl and vinyl iodides led to the formation of primarily naphthalenes **1.278**. In addition, reactions with aryl and vinyl bromides typically provided products **1.277** in low yields,[67a-b] and there were no reports of reactions with aryl chlorides.



1.276 **1.277** **1.278**

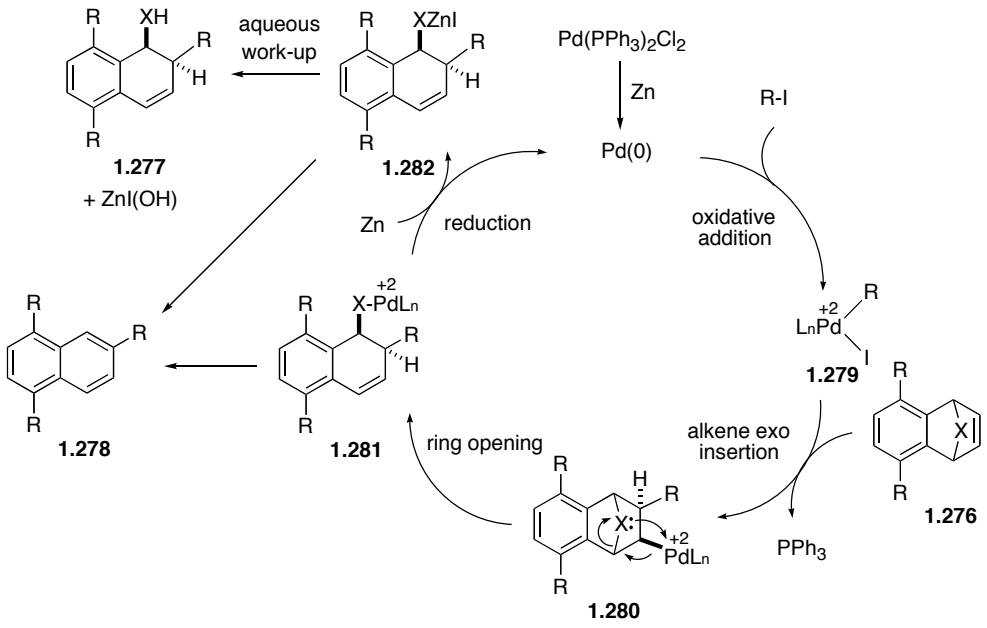
X = O, NCO_2Me For electron rich aryl and vinyl iodies: major minor

R = OMe, H For electron deficient aryl and vinyl iodides: minor major

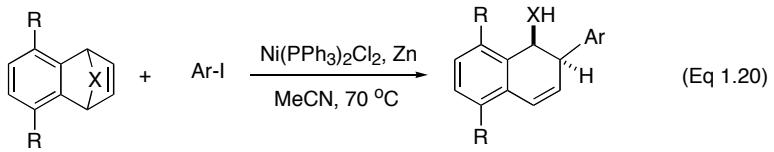
A possible mechanism for the palladium-catalyzed ring opening reaction is shown in Scheme 1.38.[67b] The first step of the catalytic cycle involves the reduction of Pd(II) to Pd(0) by zinc. This is followed by oxidative addition of Pd(0) to the organic halide to generate the organopalladium(II) intermediate **1.279**, which then coordinates to the bicyclic alkene **1.276** on the *exo* face and delivers the aryl or vinyl group to one of the olefin carbons to generate intermediate **1.280**. It is important to note that chelation of metal by the olefin and the heteroatom (i.e., oxygen or nitrogen) of **1.276** helps contribute to the high *exo* selectivity.[66b] Since no *cis*-β-hydrogens are present, β-hydride elimination

is not possible. As a result, β-heteroatom (oxygen or nitrogen) elimination occurs to generate ring-opened intermediate **1.281**, which gives zinc salt **1.282** and regenerates the palladium(0) catalyst upon reduction with zinc. Hydrolysis of the zinc salt **1.282** upon aqueous work-up liberates the final product **1.277**. Further elimination of a water or amine molecule from intermediates **1.281** or **1.282** gives the naphthalene by-products **1.278**. $ZnCl_2$ presumably acts as a Lewis acid associated with the bridging oxygen to facilitate β-heteroatom elimination.

Scheme 1.38



A few years later, Cheng reported a similar ring opening methodology using a nickel catalyst (Eq 1.20).[67c] The nickel-catalyzed reaction was more active and able to promote the ring opening of diverse oxabicyclic [2.2.1] substrates. However, the scope of reaction was limited to electron rich aryl iodide substrates. The use of electron deficient aryl iodides provided lower yields of products **1.277**, and the use of phenyl bromide only gave the corresponding product in less than 20% yield.



1.276

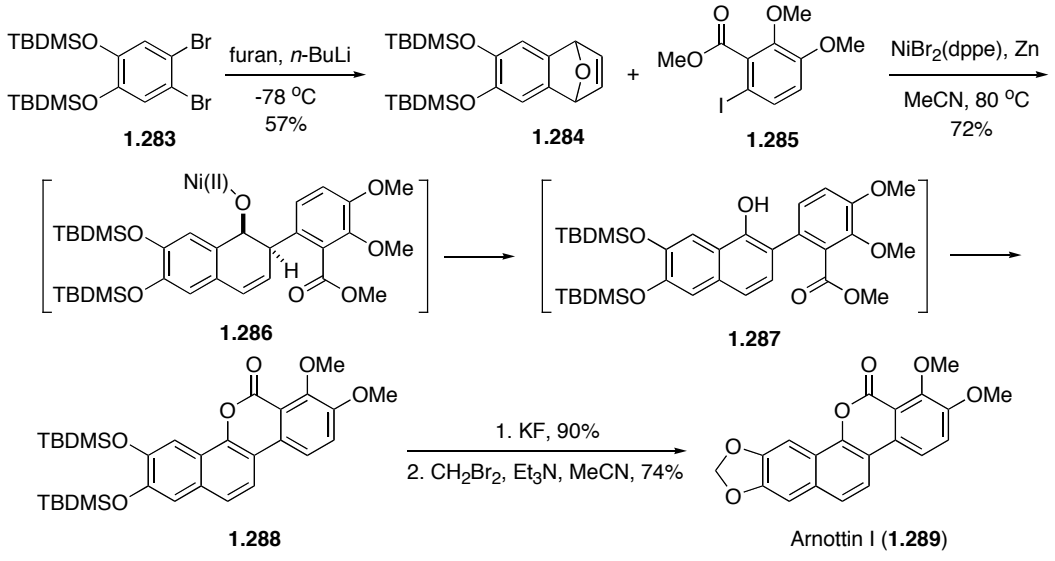
X = O, NCO_2Me
R = OMe, H

1.277

(Eq 1.20)

Cheng reported the total synthesis of arnottin I (**1.289**) using the ring opening strategy in 2006 (Scheme 2.6).[82] The Diels-Alder reaction of the benzyne derived from elimination of dibromobenzene **1.283** with furan gave the oxabenzonorbornadiene **1.284**. The nickel-catalyzed ring opening of **1.284** with methyl 2,3-dimethoxy-6-iodobenzoate (**1.285**) gave the dihydronaphthol intermediate **1.286**, which underwent oxidation with Ni(II) and intramolecular esterification *in situ* to yield benzocoumarin **1.288** and regenerate Ni(0).[83] Removal of silyl groups with KF followed by alkylation with CH_2Br_2 furnished arnottin I (**1.289**).

Scheme 1.39



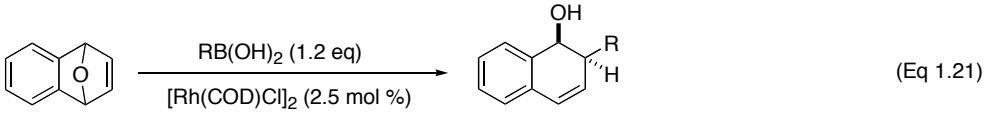
1.283 **1.284** **1.285**

1.286 **1.287**

1.288 Arnottin I (**1.289**)

1.9.1.C Using Aryl and Vinyl Boronic Acid for Ring Opening Reactions

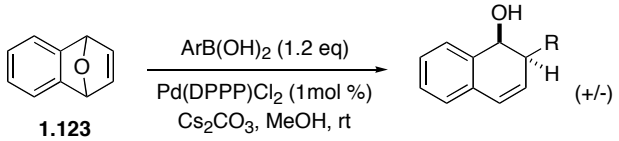
Lautens developed an asymmetric ring opening reaction of oxabenzonorbornadienes using alkenyl and aryl boronic acids (Eq 1.21).[68b] These reactions proceeded in good yields, with excellent enatio- and diastereoslectivities. However, couplings with particular heteroarylboronic acids were often problematic, giving unopened addition products and oligomeric products. They only provided few examples about the ring opening of oxabenzonorbornadienes, and the scope of the reaction was not well reported.



1.123 (Eq 1.21)

1.290a: R = *trans*-C_4H_9CH=CH, 93%, 88% ee
1.290b: R = C_6H_5, 78%, 92% ee

Lautens developed a palladium-catalyzed ring opening of oxabenzonorbornadienes with aryl boronic acid (Eq 1.22).[68c] He founds that palladium catalysts are more reactive than Rhodium catalysts. The coupling of **1.123** with a variety of aryl and heteroaryl boronic acid proceeded in excellent yield at room temperature, including electron-rich and -deficient aryl boronic acids. The palladium catalyst is air-stable and compatible with undistilled solvents. However, the use of bidentate chiral phosphine ligands only provided moderate enantioselectivities. The feasibility of the couplings with vinyl boronic acids was not reported yet. When the coupling strategy was extended to azabenzonorbornadienes, reactions required elevated temperatures.



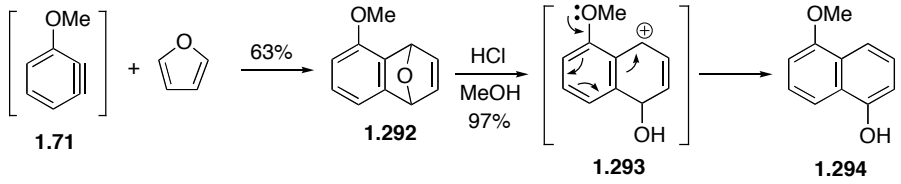
1.123 (+/-) (Eq 1.22)

1.291a: R = *p*-Br-C_6H_4, 83%
1.291a: R = *o*-MeO-C_6H_4, 74%
1.291a: R = *m*-MeO-C_6H_4, 86%
1.291a: R = *o*-CH_3CO-C_6H_4, 83%

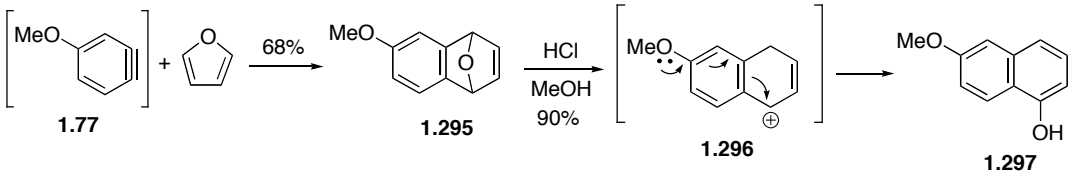
1.9.2 Acid-Catalyzed Ring Opening of Oxabenzonorbornadienes

Acid-catalyzed ring opening of oxabenzonorbornadienes, derived from cycloadditions of substituted benzynes and furans, give a variety of naphthols.[45b] Some of these ring opening reactions are highly regioselective. For example, methoxybenzynes **1.71** and **1.77** underwent facile cycloaddition with furan to provide cycloadducts **1.292** and **1.295**, respectively (Scheme 1.40 and 1.41).[45b] Under the acidic conditions, protonation of epoxide oxygens followed by opening of bridge rings tends to generate more stable carbocation intermediates **1.293** and **1.296** due to the resonance stabilization derived from electron-donating methoxy groups on the aromatic ring. Aromatication of these intermediates thus provides naphthols **1.294** and **1.297**.

Scheme 1.40



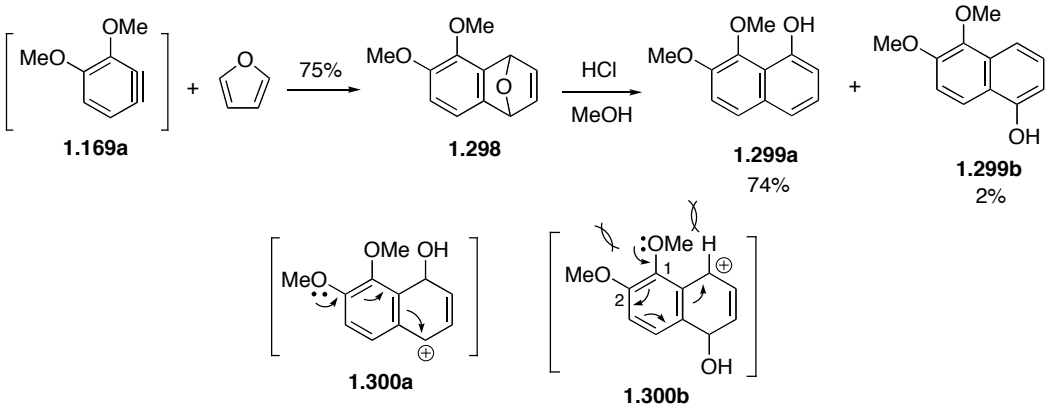
Scheme 1.41



The ring opening of cycloadduct **1.298** deserved some comments. The major product **1.299a** would arise from the cabocation **1.300a**, whereas the minor product **1.299b** would arise from the cabocation **1.300b**. For the carbocation **1.300b**, presumably the *peri*-methoxy group on C1 is out of the plane of the conjugated system because of steric hindrance by the methoxy group on C2 and proton on secondary carbocation. The

resonance stabilization derived from the methoxy group on C1 is weak and, thus, the reaction provides minor product **1.299b**.

Scheme 1.42

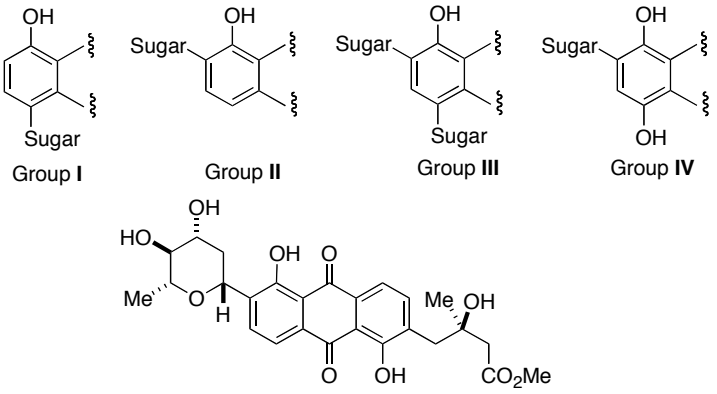


1.10 PRIOR WORK IN MARTIN GROUP

1.10.1 Synthesis of *C*-Aryl Glycosides using Symmetric Benzynes

C-aryl glycoside antibiotics comprise an important group of the *C*-glycoside family of natural products.[84,85,86] Because of their range of significant biological activities and resistance to enzymatic hydrolysis, *C*-aryl glycosides have attracted considerable interest. There are four common structural types of *C*-aryl glycosides (Groups I-IV), which have been classified on the basis of the substitution pattern of the sugar residue(s) and the hydroxyl group(s) on the aromatic core (Figure 1.6).[87] Vineomycinone B_2 methyl ester (**1.301**) represents a member of this family. Hence, one of the significant challenges presented by these complex antibiotics lies in the design and development of a unified strategy for the synthesis of the four major types of *C*-aryl glycosides.[88]

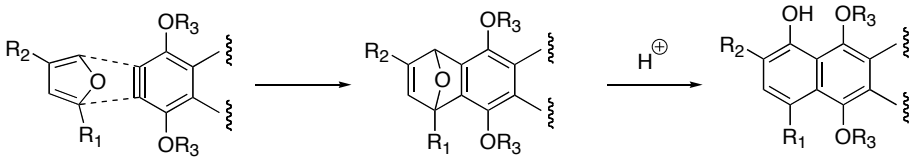
Figure 1.6



Vineomycinone B_2 methyl ester (**1.301**)

After considering a number of novel approaches to *C*-aryl glycosides, we were interested in the pathway that is summarized in Scheme 1.43. The acid-catalyzed rearrangement of compounds related to oxabenzonorbornadienes **1.304**, which are formed by cycloadditions of furans and benzynes, was well-known to give naphthols.[89] However, 2-glycosyl furans have never been exploited as dienes in such processes. To establish the underlying feasibility of this new approach to *C*-aryl glycosides our group embarked on a series of model studies.[90a]

Scheme 1.43



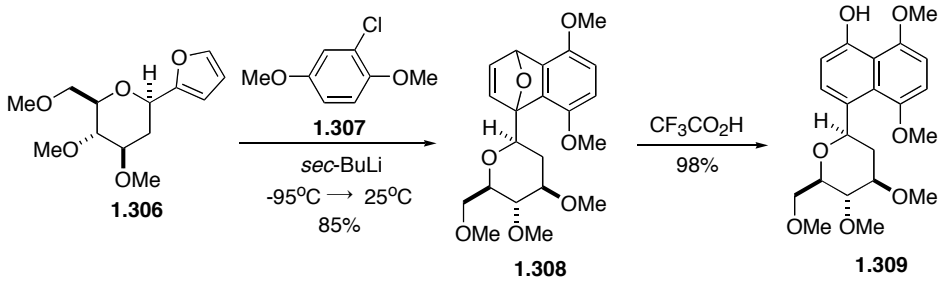
1.302 **1.303** **1.304** **1.305**

Group **I**: R_1 = sugar; R_2 = H
Group **II**: R_1 = H; R_2 = Sugar
Group **III**: R_1 = R_2 = sugar
Group **IV**: R_1 = OH; R_2 = sugar

Our first initiative was to evaluate whether a 2-glycosyl furan would undergo a Diels-Alder reaction with a benzyne. After some preliminary experimentation using

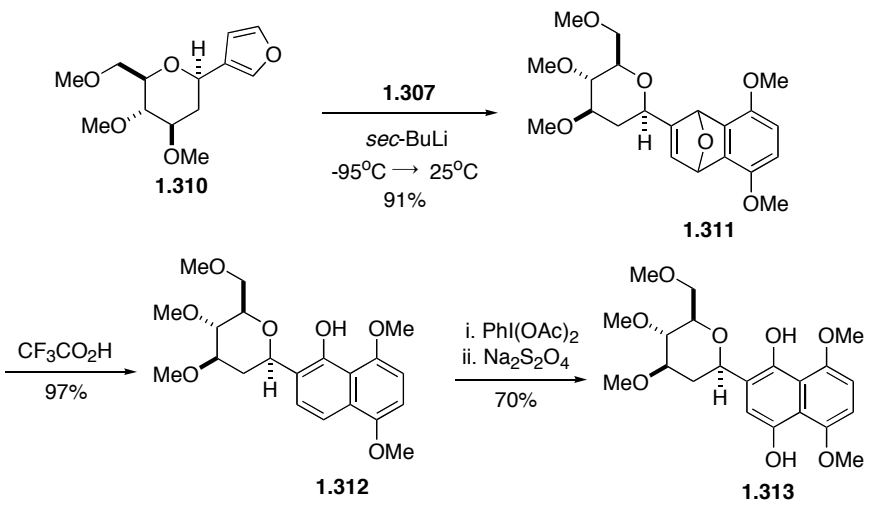
various bases and temperatures, we found that **1.307** could be efficiently deprotonated *ortho* to the chloro group using *sec*-BuLi at -95 °C (Scheme 1.44). After furan **1.306** was added, the mixture was allowed to warm slowly to room temperature during which time benzyne generation occurred and subsequent cycloaddition with furan provided **1.308**. Acid-catalyzed rearrangement of **1.308** then furnished the Group I *C*-aryl glycoside representative **1.309** as a single diastereomer in excellent overall yield.

Scheme 1.44



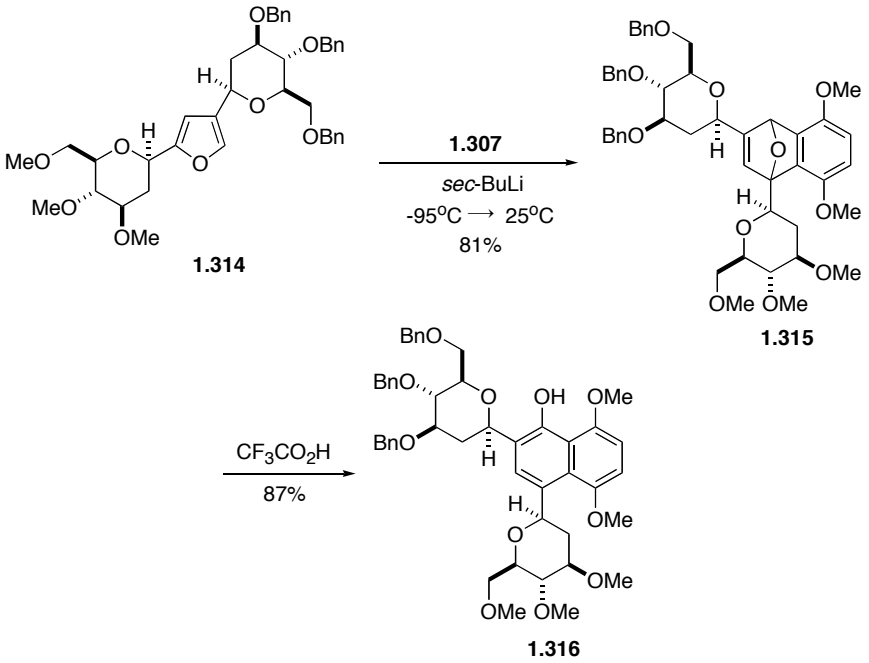
Similarly, we found that cycloaddition of the 3-glycosyl furan **1.310**[91,92] with 1,4-dimethoxybenzyne gave **1.311** (Scheme 1.45). The acid-catalyzed rearrangement of **1.311** provided a readily separable mixture (10:1) of the Group II *C*-aryl glycoside model **1.312**, which was obtained as a single diastereomer, and the isomeric *m*-substituted product. Oxidation of **1.312** with $PhI(OAc)_2$ and reduction of the quinone thus obtained with $Na_2S_2O_4$ delivered the Group IV *C*-aryl glycoside **1.313**.

Scheme 1.45



Having demonstrated that representative *C*-aryl glycosides of Groups I (i.e., **1.309**), II (i.e., **1.312**), and IV (i.e., **1.313**) were accessible, preparing a more challenging Group III *C*-aryl glycoside model was undertaking. Cycloaddition of dimethoxybenzyne with 2,4-diglycosyl furan **1.314**, which was prepared as a mixture (ca. 6:1) of epimers, provided cycloadduct **1.315**, which underwent facile acid-catalyzed rearrangement to provide the Group III *C*-aryl glycoside model **1.316** as a single diastereomer (Scheme 1.46).

Scheme 1.46



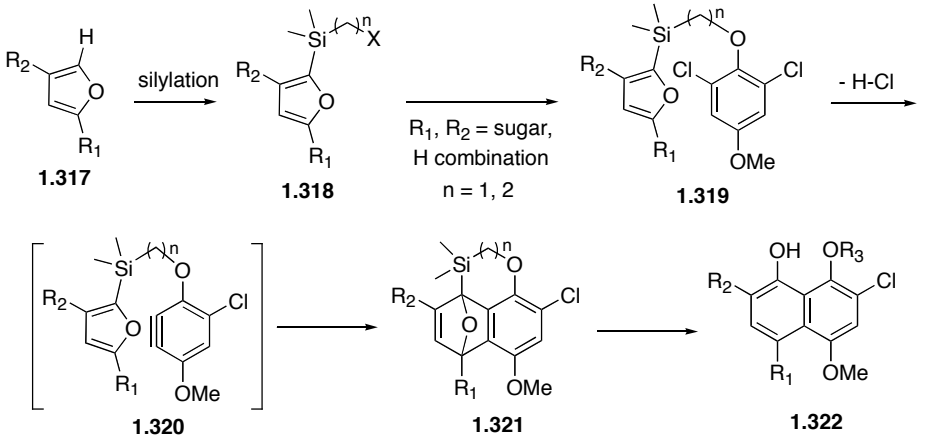
We have developed a general strategy to prepare the four major types of *C*-aryl glycosides, which involves the acid-catalyzed ring openings of the cycloadducts obtained from the Diels-Alder reaction of benzynes with glycosyl furans.[90a] Since symmetrical benzynes were universally employed as reaction partners in these studies, regiochemistry of the cycloaddition was never an issue. Although unsymmetrical benzynes are known to undergo regioselective Diels-Alder reactions,[5] such cycloadditions typically required particular benzyne precursors and diene substrates (see Chapter 1.4.3). This problem was obvious during recent work that culminated in a formal synthesis of the *C*-aryl glycoside galtamycinone.[93] Hence, to apply our methodology to the synthesis of naturally occurring *C*-aryl glycosides, to control the regiochemistry of the pivotal benzyne-furan cycloadditions thus became important. We developed another strategy that employs disposable silicon tethers to control the regiochemistry of Diels-Alder cycloadditions of substituted benzyne and glycosyl furans to provide ready access to unsymmetrical

representatives of the three major groups of *C*-aryl glycosides.[94]

1.10.2 Regioselective Synthesis of *C*-Aryl Glycosides using Silicon Tethered Benzyne-Furan Cycloadditions

Two protocols using one and two carbon atoms in the silicon tether were developed as outlined in Scheme 1.47.[90d] Regioselective metalation of glycosyl furan derivatives **1.317** followed by trapping the resultant anion with an appropriate chlorosilane and refunctionalization as needed leads to the silanes **1.318**, which are coupled with halophenols to provide **1.319**. Selective deprotonation of **1.319** generates the benzynes **1.320**, which undergoes intramolecular Diels-Alder reaction with tethered furan to furnish the cycloadducts **1.321**. On the basis of the prior art of Rickborn and Stork,[95] we discovered that fluoride would induce the cleavage of the silicon-carbon bonds in **1.321** to give intermediates that could undergo acid-catalyzed opening of the oxabenzonorbornadiene ring to deliver the glycosyl naphthols **1.322** (R^3 = H or Me), depending on the nature of the tether and the condition used to effect its removal.

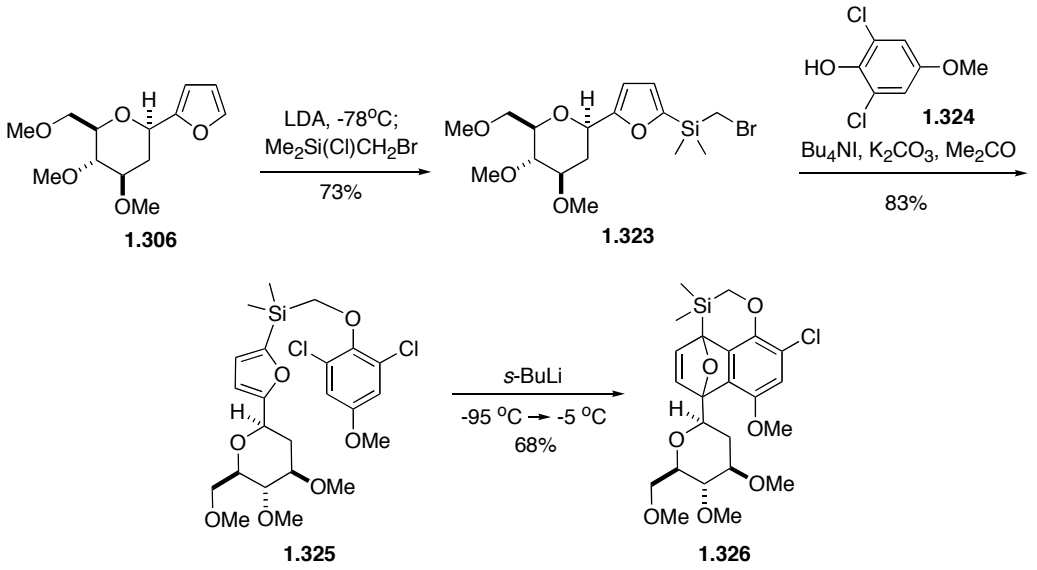
Scheme 1.47



The use of silicon tethers to access Group I *C*-aryl glycosides may be exemplified

by two related strategies that differ in the number of carbon atoms that are present in the connecting chain. In the first of these, the known glycosyl furan **1.306** was converted into the furylsilane **1.323** by sequential metalation (LDA, THF, -78 °C) and trapping the resultant anion with bromomethylchlorodimethylsilane (Scheme 1.48). *O*-Alkylation of 2,6-dichloro-4-methoxyphenol (**1.324**)[96] with **1.323** then furnished the Diels-Alder precursor **1.325**. When **1.325** was treated with *s*-BuLi in THF at -95 °C, facile deprotonation *ortho* to one of the chlorine atoms occurred. The resultant anion underwent elimination upon warming to generate an intermediate benzyne that then cyclized *via* an intramolecular Diels-Alder reaction with the tethered furan to provide a mixture of diastereomeric cycloadducts **1.326**.

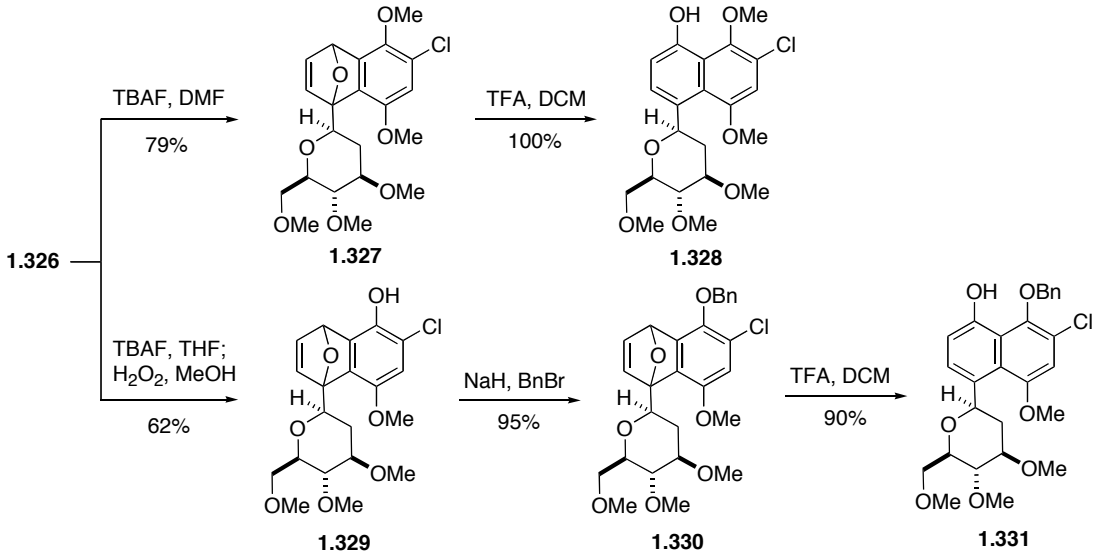
Scheme 1.48



Two methods were developed for converting the cycloadduct **1.326** into substituted naphthols. The first method was to cleave both carbon-silicon bonds in **1.326** using excess Bu_4NF (TBAF) in DMF to afford dimethyl ether **1.327**, which underwent acid-catalyzed ring opening to furnish **1.328**, a representative *C*-aryl glycoside of Group I

(Scheme 1.49). For the second method, only the bridgehead carbon-silicon bond in **1.326** was cleaved upon treatment with TBAF in THF; subsequent Tamao oxidation gave the phenol **1.329**.[97,98] *O*-Alkylation of **1.329** followed by acid-catalyzed ring opening delivered **1.331** in which each of the phenolic oxygens is differentiated for subsequent transformations.

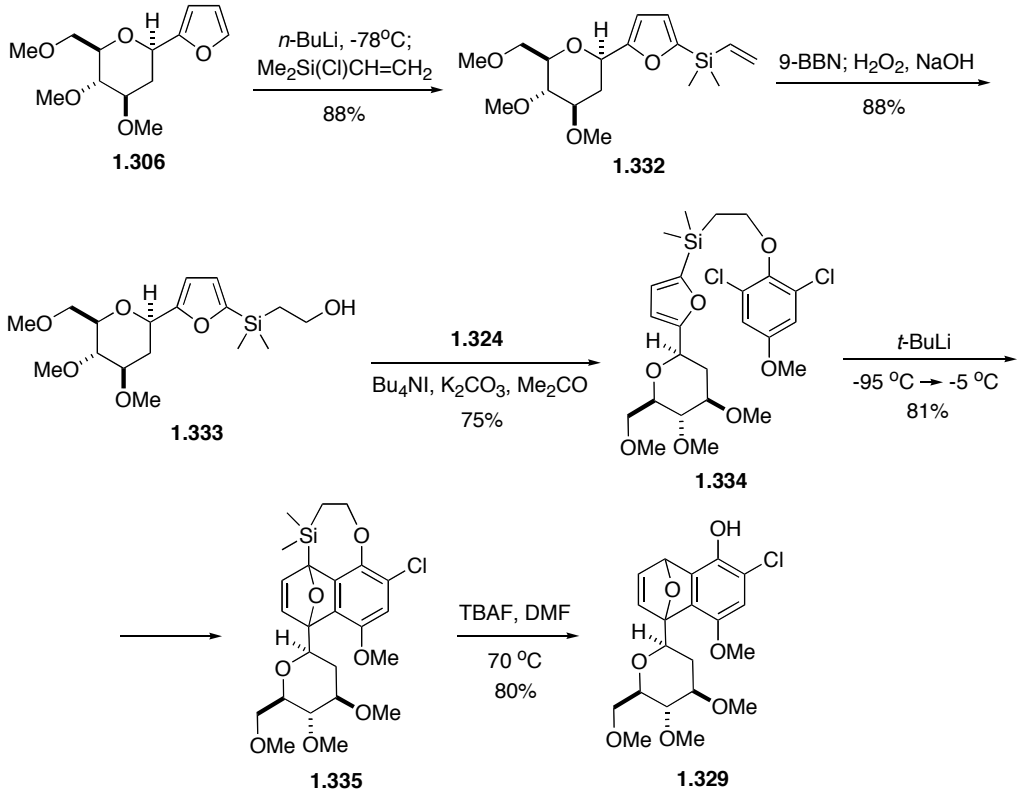
Scheme 1.49



Because of competing nucleophilic attack on silicon, *O*-alkylations of other phenols with bromomethylsilanes such as **1.323** may be problematic.[99] We developed a solution to this problem that uses a silicon tether containing an additional carbon atom. Thus, **1.306** was converted into the vinylsilane **1.332** by metalation and trapping the resultant anion with chlorodimethylvinylsilane (Scheme 1.50). Regioselective hydroboration of **1.332** followed by oxidation (9-BBN, THF; H_2O_2, NaOH)[100] provided alcohol **1.333**. Mitsunobu coupling[101] of **1.333** with **1.324** then gave cycloaddition precursor **1.334**. Deprotonation of **1.334** with *t*-BuLi led to the formation of an intermediate benzyne that underwent cycloaddition with tethered furan to deliver **1.335**.

Treatment of **1.335** with TBAF in DMF at 70 °C provided the tether-cleaved product **1.329** in 80% yield.[102]

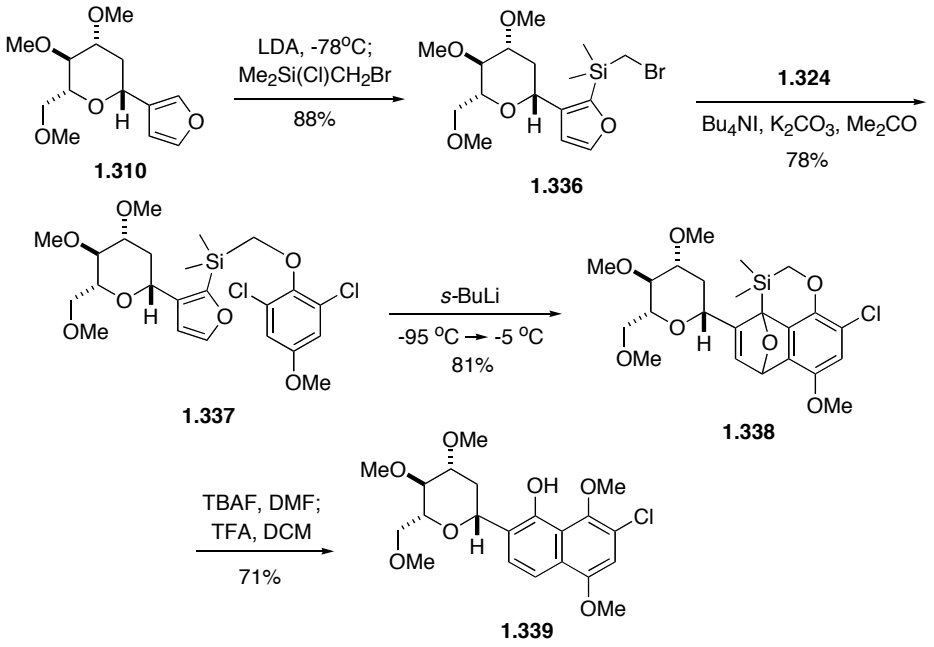
Scheme 1.50



Having developed an effective regioselective strategy for preparing Group I *C*-aryl glycosides, the next task was to extend this approach to representative glycosides of Groups II and III. Toward this end, the known glycosyl furan **1.310** was metalated (LDA, THF, -78 °C) and reacted with bromomethylchlorodimethylsilane to provide **1.336** (Scheme 1.51). *O*-Alkylation of phenol **1.324** with **1.336** afforded Diels-Alder precursor **1.337**. Deprotonation of **1.337** occurred selectively on the phenyl ring, and the benzyne that formed upon warming cyclized to provide a mixture of diastereomeric cycloadducts **1.338** in 91% yield. Cleavage of both carbon-silicon bonds using TBAF in DMF

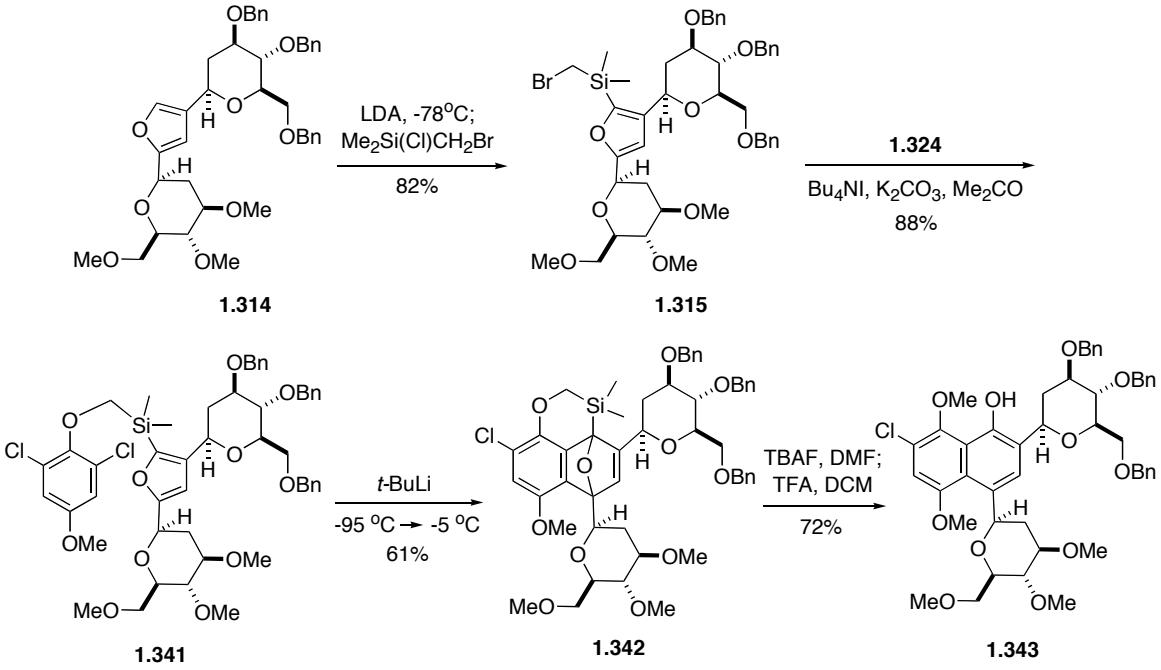
followed by ring opening upon exposure to TFA afforded naphthol **1.339** as a single isomer.

Scheme 1.51



A regiochemical controlled entry to Group III *C*-aryl glycosides commenced with converting the glycosyl furan **1.314** into the furylsilane **1.315** *via* metalation followed by silylation (Scheme 1.52). *O*-Alkylation of the phenol **1.324** with **1.315** generated **1.341**, which underwent benzyne formation and cycloaddition upon treatment with *t*-BuLi to give a mixture of diastereomeric cycloadducts **1.342**. Complete cleavage of the carbon-silicon bonds followed by acid-catalyzed ring opening provided the Group III *C*-aryl glycoside model **1.343** as a single diastereomer.

Scheme 1.52



We have exploited intramolecular benzyne-furan cycloadditions for the synthesis of unsymmetrical representatives of the three major groups of *C*-aryl glycosides. The regiochemical outcomes in these Diels-Alder reactions were controlled by using disposable silicon tethers to link the reacting benzynes and glycosyl furans. The application of this novel methodology to the synthesis of vineomycinone B_2 methyl ester will be illustrated in Chapter 4.

1.11 CONCLUSION

It should be apparent from the previous discussion that aryne chemistry has been widely used in synthetic organic chemistry, and there are considerable reports in the application of these methodologies to the synthesis of natural products. Although a vast amount of aryne chemistry has been accomplished, there still exists the potential to extend and improve upon what has been reported.

The regioselective Diels–Alder reactions of benzynes with dienes posed a significant challenge. These reactions typically required particular substituents on substrates to inductively direct the regiochemistry of cycloadditions, otherwise, cycloadditions provided a poor ratio of regioisomers (see Chapter 1.4.3). In the context of extending the regioselective cycloadditions to more general benzyne and furan substrates, our group developed a general strategy to control the regiochemical outcome of these Diels–Alder reactions using compounds in which the benzyne precursors and the reactant furans were linked with disposal silicon tethers, which was employed in the synthesis of asymmetric *C*-aryl glycoside models. Wage also demonstrated regioselective intramolecular Diels-Alder cycloaddtions of furans with tethered benzynes for the total synthesis of natural products. However, applications of the intramolecular Diels-Alder cycloadditions of benzynes with furans for the assembly of the *C*-aryl glycosyl natural products have not been reported. The Chapter 4 will detail the work toward the synthesis of vineomycinone B_2 methyl ester.

Numerous procedures are effective for inducing the ring opening of oxabenzonorbornadienes, derived from Diels-Alder reactions of benzynes with furans, to give 2-substituted-1,2-dihydro-1-naphthols. Most suffer from one or more limitations associated with their efficiency, generality and/or ease of execution (see Chapter 1.9.1.A

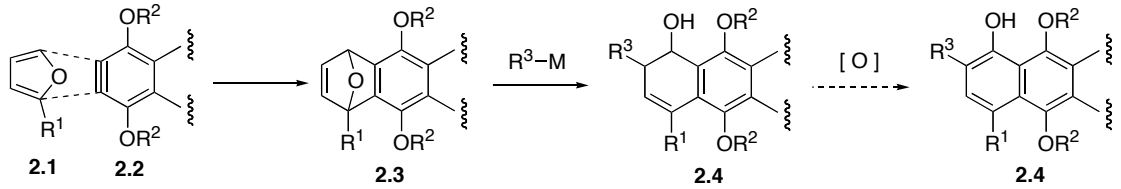
and B). However, these methodologies have never been used for the synthesis of *C*-aryl glycosides. In addition, oxidation of 2-substituted-1,2-dihydro-1-naphthols to the responding 2-substituted-1-naphthols was known to be difficult.[90a-c,e,f,105] The Chapter 2 will address the work toward the goal of developing novel methodologies for the synthesis of functionalized 2-substituted-1,2-dihydro-1-naphthols, 2-substituted-1-naphthols, and Group II *C*-aryl glycoside models.

Chapter 2. Syntheses of 2-Substituted-1,2-dihydro-1-naphthols and 2-Substituted-1-naphthols

2.1 INTRODUCTION

The synthesis of *C*-aryl glycoside antibiotics is an important focus in our research group.[90] As described in the previous chapter, we have introduced two general approaches to prepare the major groups of *C*-aryl glycosides.[90a-b] The first involves the acid-catalyzed ring opening of the cycloadducts obtained from the Diels-Alder reactions of benzynes with glycosyl furans, and the other features the silicon tether strategy to control the regiochemical outcome of the Diels-Alder reactions of substituted benzynes and glycosyl furans. In the context of developing general synthetic approaches to *C*-aryl glycosides,[84,88] we aspired to design a more concise and straightforward approach for the formation of aryl-glycosyl bonds. In the past decade, ring opening of oxabenzonorbornadienes **2.3**, derived from Diels-Alder reactions of benzynes **2.2** with furans **2.1**, with organometallic reagents to give dihydronaphthols **2.4** has been extensively studied (Scheme 2.1).[66] We hoped that using glycosyl organometallic reagents for the ring opening reactions followed by oxidation of dihydronaphthol derivatives would provide *C*-aryl glycosides.

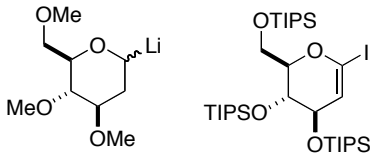
Scheme 2.1



Dr. Omar Lopez, a former postdoctoral associate of the Martin Group had conducted a number of experiments to determine whether glycosyl carbanions **2.5** (Figure 2.1) might induce the S_N2' opening of oxabenzonorbornadienes related to **2.3**.[103]

However, significant quantities of ring-opened products were not isolated. While the possibility remains that such reactions might prove useful, we hoped that metal-catalyzed ring opening reactions might provide opportunities to generate aryl-glycosyl bonds.[66] However, glycosyl derivatives had never been used in such transformations, and the feasibility of oxidizing the intermediate, electron-rich dihydronaphthols efficiently to the corresponding naphthols without accompanying dehydration was uncertain.

Figure 2.1



2.5 **2.6**

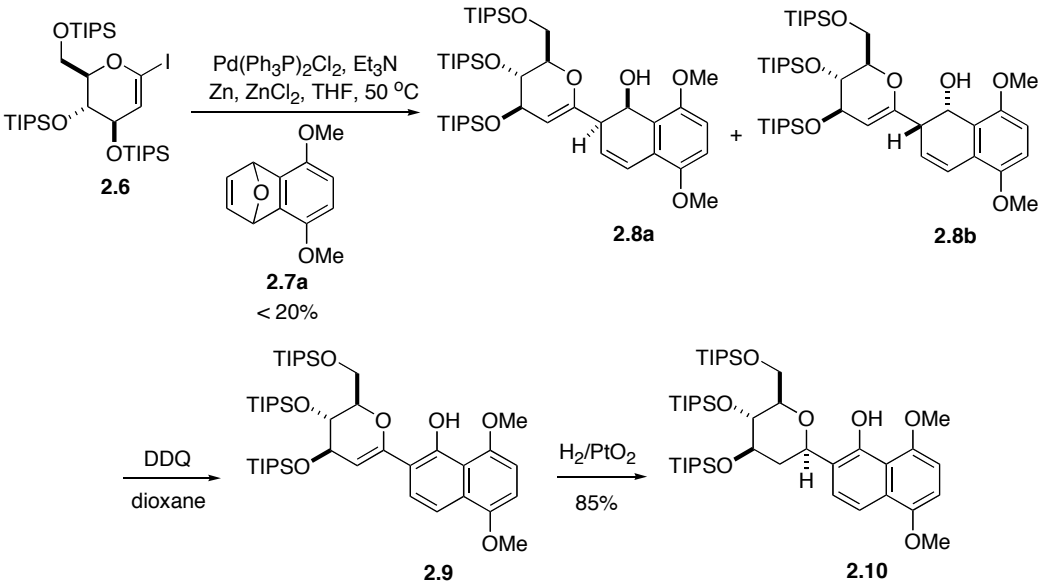
Prior to investigating a reliable metal-catalyzed ring opening reaction, an appropriate glycal substrate needs to be considered first. Iodo glycal **2.6** could be a suitable substrate since it can be synthesized easily from commercially available tri-*O*-acetyl-D-glucal in 3 steps.[104] Although numerous procedures for inducing the ring opening of oxabenzonorbornadienes are known, most suffer from one or more limitations associated with their efficiency, generality and/or ease of execution. Most relevant to transformation with the iodo glycal **2.6** are the methodologies developed by Cheng, who described the ring opening of some bicyclic alkenes with aryl and vinyl halides in the presence of palladium and nickel catalysts (see Chapter 1.9.1.B).

Since Cheng's method allowed the use of electron rich aryl and vinyl iodides for the ring opening reaction, we were encouraged to apply this protocol to the synthesis of *C*-aryl glycosides using the glycal iodide **2.6**. In our preliminary investigation, ring opening of **2.7a** with **2.6** under the same conditions reported by Cheng gave a mixture of

the diastereomeric *cis*-dihydronaphthols **2.8a** and **2.8b** in less than 20% yield, perhaps as a consequence of the instability of the glycal iodides under the reaction conditions (Scheme 2.2).

The oxidation of alcohols to ketones is one of the most frequently used reactions in organic synthesis, but examples of the oxidation of dihydronaphthols to give naphthols are rare.[90a, 105] Oxidations of substituted dihydronaphthols **2.8a**-**b** to give the corresponding aromatic compounds **2.90** were often accompanied by considerable dehydration and oxidation to give the corresponding naphthalene and quinone side products.[90a,105] Recrystallized DDQ appeared as a useful oxidant in some cases, but we found that such transformation were sometimes difficult to optimize and reproduce.[90a] Reduction of **2.9** by catalytic hydrogenation with PtO_2/H_2 then delivered the Group II *C*-aryl glycoside **2.10** as a single diastereomer.

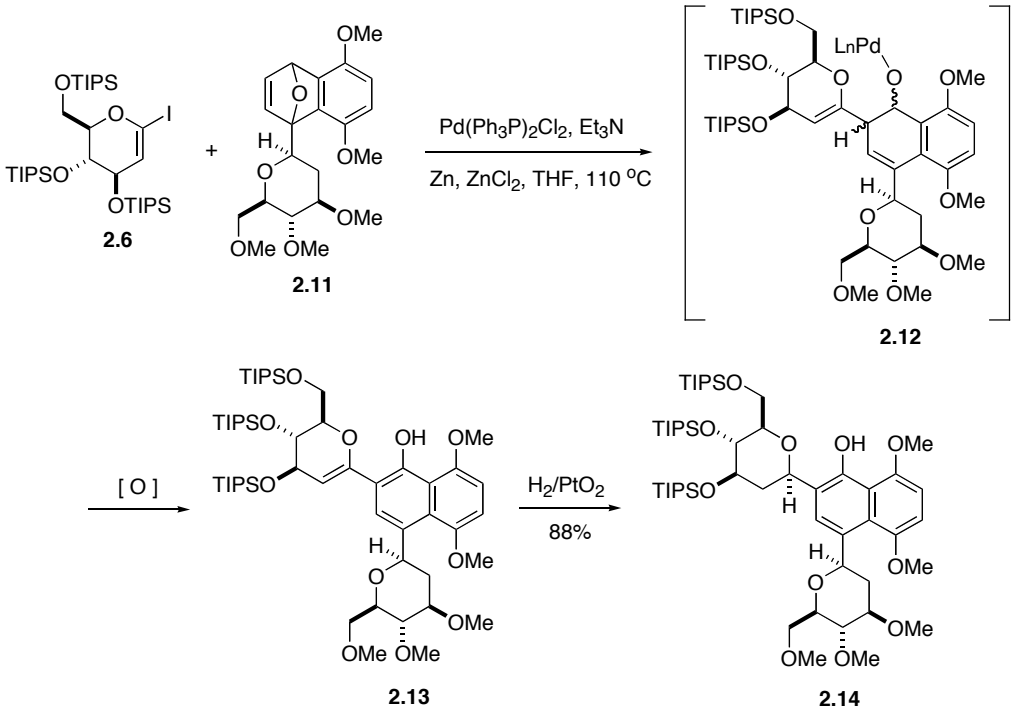
Scheme 2.2



Similarly, we found that the palladium-catalyzed ring opening of the sugar-

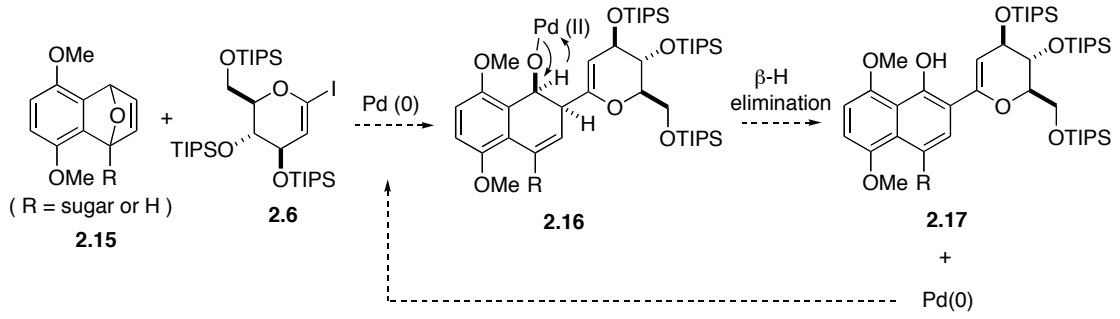
substituted cycloadduct **2.11** with **2.6** under more forcing conditions gave naphthol **2.13** (Scheme 2.3). Presumably the palladium(II)-catalyzed oxidation of dihydronaphthol intermediates **2.12** occurred to give naphthol **2.13**. Indeed, the palladium(II)-catalyzed oxidation of alcohols is well-known and has been thoroughly reviewed,[106] and several research groups have worked in this field, including Yoshida[107], Larock,[108] Stoltz,[109] Stahl,[110] Sigman,[111] Uemura[112], and Muzart.[113] A similar oxidation process was reported by Cheng, who observed that a dihydronaphthol intermediate **1.286** was oxidized by nickel to give naphthol **1.287** (Scheme 1.39). However, we were not able to reproduce the yield of **2.13** on a reasonable scale. Hydrogenation of glycosyl olefin then furnished the Group III *C*-aryl glycoside model **2.14**.

Scheme 2.3



When we explored the ring opening reactions for the synthesis of *C*-ary glycosides, we discovered that the palladium-catalyzed ring opening reaction provided dihydronaphthols **2.8a**-**b** at 50 °C (Scheme 2.2), but the reaction gave naphthols **2.13** at 110 °C (Scheme 2.3). At this point, we assumed that the palladium-catalyzed oxidation of dihydronaphthol intermediates **2.12** might require high temperatures. These results encouraged us to investigate a palladium-catalyzed, tandem reaction as shown in Scheme 2.4, that involves ring opening of oxabenzonorbornadienes **2.15** with iodo glycal **2.6** followed by oxidation of dihydronaphthol intermediates **2.16** to deliver *C*-aryl glycosides **2.17**. This one-pot approach may avoid problems coming from the oxidation of dihydronaphthols with DDQ. Prior to developing a tandem approach for the synthesis of *C*-aryl glycosides using iodo glycal **2.6**, a methodology study was initiated to determine the feasibility of ring opening/oxidation reaction by using aryl iodides in the coupling reactions.

Scheme 2.4

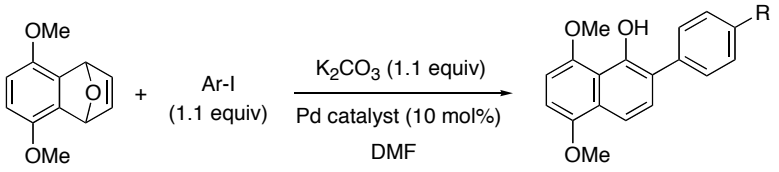


2.2 TANDEM PD-CATALYZED TANDEM RING OPENING/OXIDATION

2.2.1 Model System

In an effort to determine the optimal parameters for the palladium-catalyzed tandem reaction, we considered a combination of the reaction conditions required for palladium-catalyzed alcohol oxidations and Cheng's ring opening reaction. For example, Yoshida reported a palladium-catalyzed oxidation of primary and secondary alcohols using phosphine ligand in DMF or THF in the presence of a base such as K_2CO_3.[107] Hence, we started our studies using the combined conditions of and Yoshida [$Pd(PPh_3)_4$, DMF, THF, K_2CO_3] and Cheng (THF, $ZnCl_2$). Treatment of oxabenzonorbornadiene **2.7a** with phenyl iodide, K_2CO_3 in the presence of a catalytic amount of $Pd(PPh_3)_4$ in DMF at 60 °C afforded 2-phenyl-1-naphthol **2.18** in 36% yield (Table 2.1, Entry 1). Changing the solvent from DMF to THF resulted in a lower yield of product **2.18** (Entry 2). The yield of **2.18** increased to 58% when the temperature was raised to 110 °C (Entry 3). Addition of $ZnCl_2$, which was reported as an effective additive by Cheng, to the reaction mixture provided lower yields of **2.18** (Entries 4-5). Coupling of **2.7a** with *p*-iodoanisole and *p*-iodophenol under the similar conditions as Entry 3 provided the corresponding naphthols **2.19** and **2.20**, respectively, in moderate yields (Entry 6-7). Interestingly, using a 2:1 ratio of $Pd(PPh_3)_4$ and $Pd_2(dba)_3 \cdot CHCl_3$ as the catalyst, which has a lower ratio of phosphine to palladium, increased the yield of **2.20** to 71% (Entry 8). These results revealed that higher temperatures (90-110 °C) were necessary to achieve the tandem ring opening/oxidation reaction.

Table 2.1 Palladium-Catalyzed Tandem Reaction



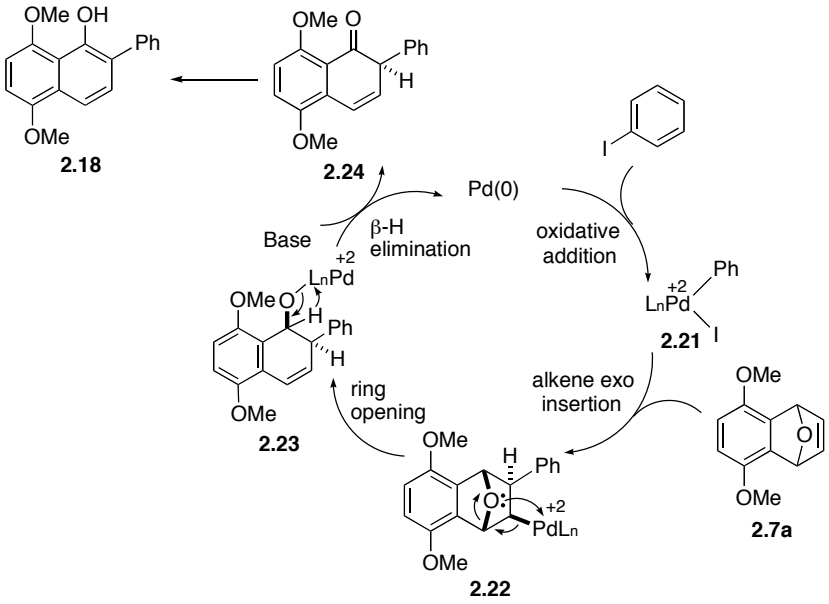
2.18: R = H
2.19: R = OH
2.20: R = OMe

Entry	Ar-I	Pd Catalyst	Temp (°C)	Yield (%)[a]
1	PhI	$Pd(PPh_3)_4$	60	36
2[b]	PhI	$Pd(PPh_3)_4$	60	9
3	PhI	$Pd(PPh_3)_4$	110	58
4[c]	PhI	$Pd(PPh_3)_4$	60	12
5[c]	PhI	$Pd(PPh_3)_4$	110	54
6	*p*-HO-C_6H_4-I	$Pd(PPh_3)_4$	110	41
7	*p*-MeO-C_6H_4-I	$Pd(PPh_3)_4$	110	56
8	*p*-MeO-C_6H_4-I	$Pd(PPh_3)_4$, $Pd_2(dba)_3 \cdot CHCl_3$ (2:1)	90	71

[a]Isolated yield of product after chromatography. [b]Solvent: THF. [c]Additive: $ZnCl_2$

A plausible catalytic cycle for this transformation is shown in Scheme 2.5. The first step involves oxidative addition of palladium(0) to the aryl iodide to generate the arylpalladium(II) species **2.21**, which undergoes the *exo*-selective carbopalladation at the oxabicyclic olefin to give intermediate **2.22**. β-Oxygen elimination occurs to provide palladium(II) alkoxide **2.23**. β-Hydride elimination followed by tautomerization furnishes naphthol **2.18** and regenerates palladium(0).

Scheme 2.5



In these preliminary investigations, an efficient palladium-catalyzed tandem ring opening/oxidation reaction was developed. Based on the success we had in the model system, we attempted to see whether our methodology could be applied to the synthesis of Group II and Group III *C*-aryl glycosides.

2.2.2 Synthesis of *C*-Aryl Glycosides

Efforts toward the synthesis of Group II *C*-aryl glycosides *via* Pd-catalyzed tandem coupling with iodo glycal **2.6** are summarized in Table 2.2. A variety of palladium complexes, ligands, solvents, and bases were examined. Unfortunately, all the conditions screened provided *C*-aryl glycoside **2.10** in less than 20% yield as well as a significant amount of polar by-products. In general, the use of amine bases led to naphthalene **2.25**, while use of inorganic bases gave only trace amounts of **2.10** and **2.25**.

Table 2.2 General Results of Pd-Catalyzed Tandem Reaction with Glucal Iodide

2.7a **2.6** **2.10** **2.25**

Pd Catalyst	Solvent	General Results
$Pd(OAc)_2$, PPh_3 (1:2)	DMF or Toluene	(1) Amine bases (NEt_3, *i*-Pr_2NEt, Cy_2NMe, PMP): **2.25** (2) Inorganic bases (K_2CO_3, NaOAc, Cs_2CO_3 or K_3PO_4): **2.10** (trace), **2.25** (trace)
$Pd(OAc)_2$, TFP[a] (1:2)	DMF or DMA	
$Pd(OAc)_2$, DPPP (1:2)	DMF	
$Pd(OAc)_2$, DPPE (1:2)	DMF	
$Pd_2(dba)_3 \cdot CHCl_3$, TFP (1:2)	DMF	
$Pd_2(dba)_3 \cdot CHCl_3$, PPh_3 (1:2)	DMF	
$Pd_2(dba)_3 \cdot CHCl_3$, $Pd(PPh_3)_4$ (1:2)	DMF	
$Pd_2(dba)_3 \cdot CHCl_3$, $Pd(P(t\text{-}Bu)_3)_2$ (1:2)	dioxane or DMF	
$Pd_2(dba)_3 \cdot CHCl_3$	DMF	
$Pd(PPh_3)_4$	DMF	
Palladacycle[b]	DMA	

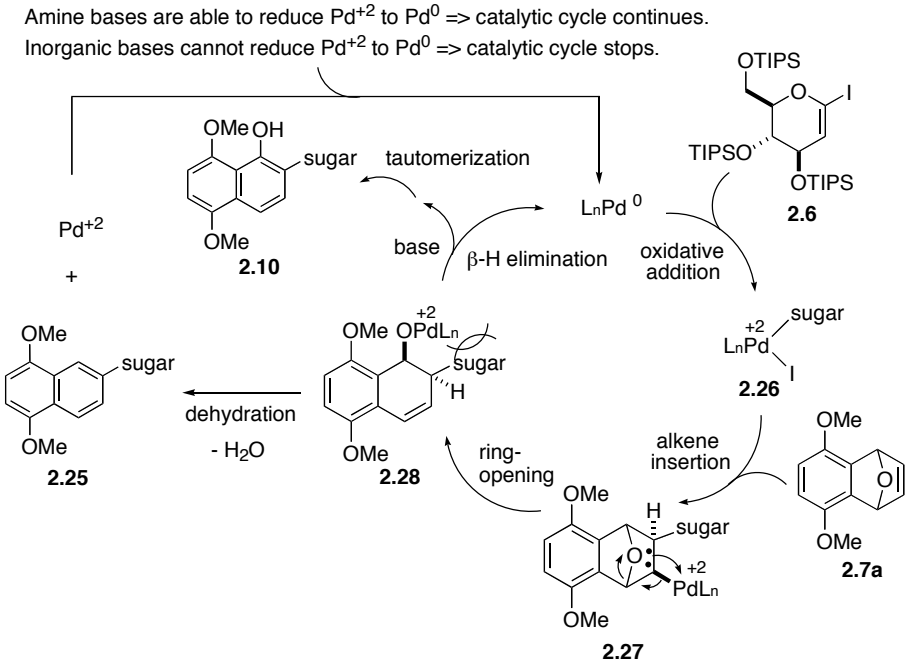
[a] TFP = tri(2-furyl)phosphine

[b] Palladacycle = di(*m*-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl] palladium(II)

There are three possible reasons to explain the low yield of naphthol **2.10** in these reactions. The first is the steric effect. The hindered sugar group, β to the palladium alkoxide, may retard the coordination of hydrogen for β-H elimination (see **2.28** in Scheme 2.6).[114] Another reason is a competitive side reaction, involving the palladium(II)- and/or base-catalyzed dehydration of intermediate **2.28** to give the naphthalene by-product **2.25**; this pathway may compete with β-H elimination. The last reason involves the base. Both Sigman and Stahl have reported that increasing the

concentration of amine bases results in substantial diminution of the catalytic rate, reflecting inhibition of palladium-catalyzed alcohol oxidation.[110b,111a]

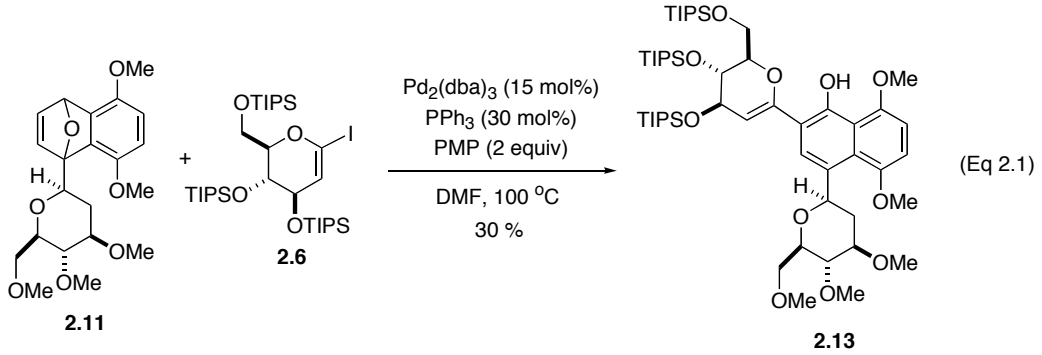
Scheme 2.6



If β-hydride elimination is slower, dehydration may proceed to generate naphthalene **2.25** and palladium(II). Subsequently, amine bases may reduce palladium(II) to palladium(0),[106b] which restarts the catalytic cycle (Scheme 2.11). However, inorganic bases, such as K_2CO_3 and K_3PO_4, cannot reduce palladium(II) to palladium(0). So, the catalytic cycle stops and only provides trace amount of **2.10** and **2.25**.

The ring opening of glycosyl oxabenzonorbornadiene **2.11** with iodo glycal **2.6** was studied for the synthesis of Group III *C*-aryl glyclosides (Eq 2.1). After extensive screening of various combinations of palladium precatalysts [$Pd(OAc)_2$, $Pd_2(dba)_3$, $Pd(PPh_3)_4$], ligands [PPh_3, P(*t*-Bu)$_3$, BINAP, P(OMe)$_3$, TFP], solvents (DMF, NMP), and bases [PMP (1,2,2,6,6-pentamethylpeperidine), *i*-Pr_2NEt, K_2CO_3], we discovered that the

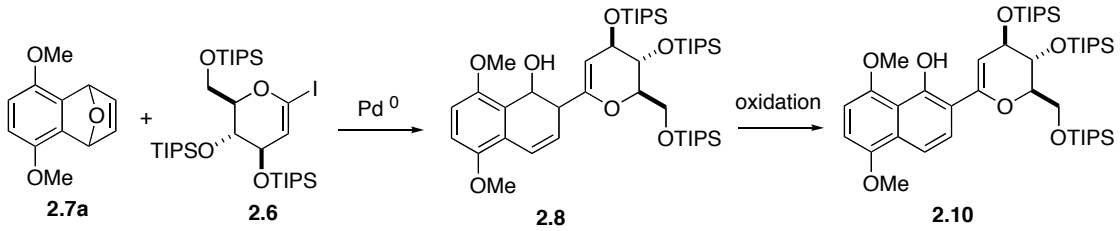
combination of $Pd_2(dba)_3$, PPh_3, and PMP in DMF at 100 °C was the most effective. However, the optimized conditions only provided **2.13** in only 30% yield, lower than that reported by Lopez.



2.2.3 A Revised Two-Step Approach

Although a model palladium-catalyzed tandem coupling reaction allowed the preparation of 2-aryl-1-naphthols, application to the synthesis of Group II and Group III *C*-aryl glycosides did not initially provide any promising results. In the context of solving the various problems associated with the efficiency of one-pot tandem coupling, we decided to adopt an alternative, two-step pathway toward the synthesis of *C*-aryl glycosides *via* the ring opening of oxabenzonorbornadiene **2.7a** and subsequent oxidation of the resultant dihydronaphthols **2.8** (Scheme 2.7).

Scheme 2.7



In the preliminary experiments shown in Scheme 2.2 and 2.3, the palladium-catalyzed ring opening reactions provided ring-opened products in lower yields, which indicated that Cheng's conditions67[a] might not be optimal. The model tandem coupling in Table 2.1 showed that DMF was superior to THF, and $ZnCl_2$ was not a necessary additive. These discoveries seemed to constitute a useful point of embarkation for future investigations. Since a number of parameters may affect the ring opening of oxabenzonorbornadienes, we decided to optimize reaction conditions using simple aryl and vinyl halides as substrates, and again explore oxidation conditions for the conversion of dihydronaphthols to naphthols. After we gained more knowledge about ring opening and oxidation reactions, we would apply the developed conditions for the synthesis of *C*-aryl glycosides.

In Chapter 1.9.1.B, we mentioned the limitation of Cheng's ring opening protocols. The couplings with electron-rich aryl iodides provided ring-opened products in good yields.67 However, transformations involving electron-deficient aryl and vinyl iodides gave primarily naphthalenes, and reactions with aryl and vinyl bromides typically proceeded in low yield. We hoped that the new ring opening reactions might extend the scope of reactions originally reported by Cheng.

2.3 PD-CATALYZED RING OPENING REACTION

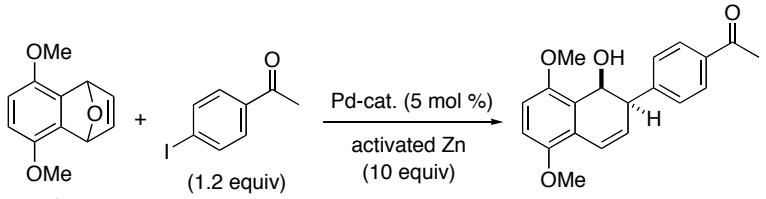
2.3.1 Pd-Catalyzed Ring Opening Reactions with Electron Deficient Aryl Iodides

In the context of preparing 2-aryl and 2-vinyl naphthol derivatives, the challenge lay in discovering milder conditions for the palladium-catalyzed ring opening reactions that would be applicable to aryl and vinyl halides that contain a wide variety of substituents. In this context, those halides bearing electron-withdrawing substituents

presented the greatest difficulty, as premature dehydration of the intermediate dihydronaphthols was known to be a significant problem.[67] We thus selected the reaction of dimethoxy oxabenzonorbornadiene **2.7a** with *p*-iodoacetophenone as the test system in which to optimize conditions for the synthesis of ring-opened dihydronaphthol **2.32a** (Table 2.3).

A variety of palladium and nickel precatalysts were examined for their ability to convert **2.7a** into **2.32a** in the presence of activated zinc powder (Table 2.3, Entries 1-8). However, only $Pd(OAc)_2/PPh_3$, $(PPh_3)_2PdCl_2$, and $Pd(PPh_3)_4$ provided **2.32a** in reasonable yields, with $Pd(OAc)_2/PPh_3$ giving the fastest rates of reaction. The nature of the solvent was important with the reactions being slower in THF, toluene, and MeCN (Entries 9-11) than in DMF. Moreover, significant amounts of the naphthalene by-product generated from the dehydration of **2.32a** were isolated when MeCN was used as solvent. Two tertiary amines 1,2,2,6,6-pentamethylpiperidine (PMP, Entry 12) and Et_3N (Entry 13) were examined as additives for the ring opening reaction. Use of PMP, which has been used to advantage in Heck reactions,[115] resulted in improved yields of **2.32a** to 95%, whereas the yield employing Et_3N was lower, in part owing to formation of naphthalene products via dehydration of the intermediate 1,2-dihydro-1-naphthols. Increasing the temperature showed the tendency to reduce the yields by increasing the amount of dehydration as a side reaction (entries 14-15). After extensive screening of various combinations of palladium and nickel precatalysts, solvents, amine bases, and temperatures, we finally discovered that ring opening of **2.7a** was highly efficient with the combination of $Pd(OAc)_2$, PPh_3, PMP, and Zn in DMF. It is worth noting that the time required for completion of reaction is ca. 3-5 times shorter if znic powder is activated by washing with 2% aqueous HCl, water, acetone and diethyl ether, and then dried in vacuum at room temperature prior to use.[116]

Table 2.3 Pd-Catalyzed Ring Opening of Oxabenzonorbornadiene **2.32a** with *p*-Iodoacetophenone[a]



Entry	Catalyst, Ligand (ratio)	Solvent	Time (h)	Yield (%)[b]
1	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	87
2	$(PPh_3)_2PdCl_2$	DMF	4.5	91
3	$Pd(PPh_3)_4$	DMF	12	85
4	$Pd(dppf)Cl_2$	DMF	16	32
5	$Pd_2(dba)_3$, dppe (1:2)	DMF	16	0
6	$(PPh_3)_2NiCl_2$	DMF	16	2
7	$NiCl_2$, dppf (1:1)	DMF	16	0
8	$NiCl_2$, dppf (1:1)	DMF	16	0
9	$Pd(OAc)_2$, PPh_3 (1:2.2)	THF	18	10
10	$Pd(OAc)_2$, PPh_3 (1:2.2)	Tol	18	3
11	$Pd(OAc)_2$, PPh_3 (1:2.2)	MeCN	8	44
12[c]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	95
13[d]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	60
14[c,e]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	3	90
15[c,f]	$Pd(OAc)_2$, PPh_3 (1:2.2)	DMF	2	64

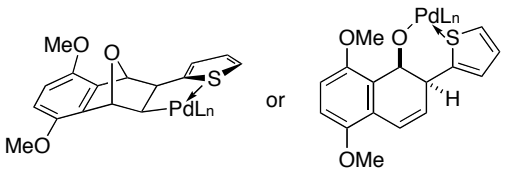
[a]Conditions: 0.05 M of **2.7a**, room temperature except as noted. [b]Isolated yield of product after chromatography. [c]PMP (0.5 eq) used as additive. [d]Et_3N (8 eq) used as additive. [e]Reaction performed at 45 °C. [f]Reaction performed at 60 °C.

2.3.2 Scope of Pd-Catalyzed Ring Opening Reaction

Having identified optimal conditions for effecting the palladium-catalyzed ring opening of **2.7a** with *p*-iodoacetophenone, the next task was to vary the nature of the halide and the oxabenzonorbornadiene to explore the scope of this process. Toward this end, a series of electron-rich and electron-deficient aryl iodides were examined and found to serve as excellent partners in ring opening reactions with **2.7a** and **2.7b** to give the corresponding dihydronaphthols **2.32a**-**2.39a** and **2.42a**-**2.44a** with high stereoselectivity and in good to excellent yields (Table 2.4). Under the mild conditions employed, only small amounts of dehydration products were isolated. The corresponding *trans*-1,2-dihydro-1-naphthols were not observed in the ^{1}H NMR spectra of the crude reaction mixtures. Ring opening of **2.7a**-**b** with aryl bromides bearing electron withdrawing and electron donating groups provide products **2.32a**, **2.33a**, **2.35a**, **2.40** and **2.42a** in good to excellent yields. In general, couplings with aryl bromides required higher temperature than aryl iodides. The difference in reactivity of aryl iodides and bromides was substantial, and it might be exploited as exemplified by selective formation of **2.37a** from *o*-bromoiodobenzene (Entry 6). Ring opening of **2.7a** with 1-bromo-2-methyl-propene gave dihydrophthol **2.41a** in good yield (Entry 13). As is typical of most palladium-catalyzed, cross coupling processes, reactions with electron-rich halides (deactivated halides) required higher temperatures than the corresponding electron-deficient halides (activated halides).[117] Moreover, coupling reactions involving mesityliodide and 2-iodothiophene required higher temperatures in order to provide good yields of products (Entry 7-8), suggesting our couplings may be sensitive to steric and coordination effects (Figure 2.2).[118] These reasons can be supported from Gouverneur's and Cheng's experiments.[118] Gouverneur found that the palladium-catalyzed coupling with iodobenzene only required 50 °C, whereas coupling with mesityliodide needed 100 °C.

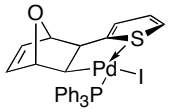
Cheng isolated a palladium complex **2.31**, showing the coordination of sulfur to palladium (Figure 2.3).

Figure 2.2



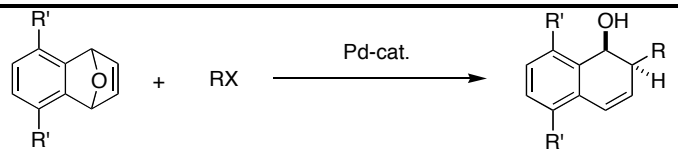
2.29 **2.30**

Figure 2.3



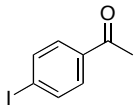
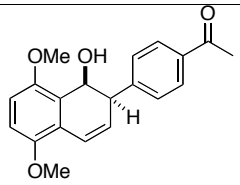
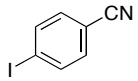
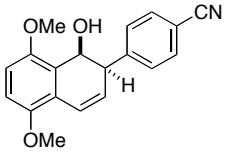
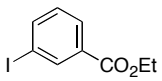
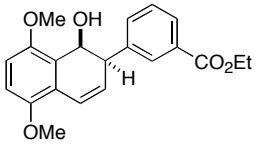
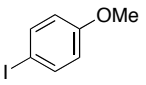
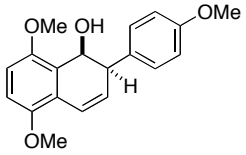
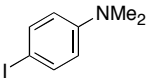
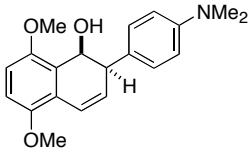
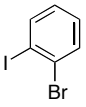
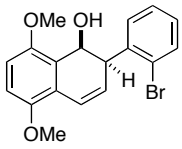
2.31

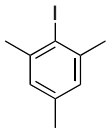
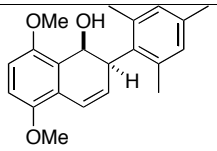
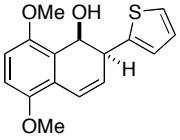
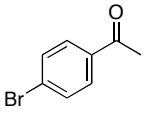
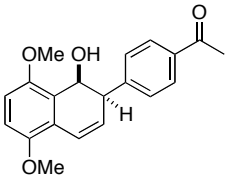
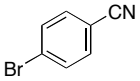
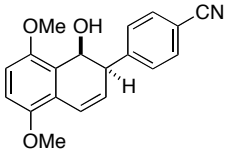
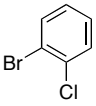
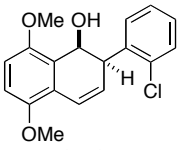
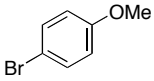
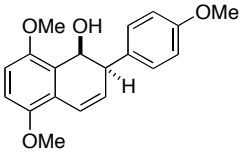
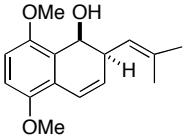
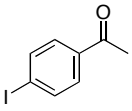
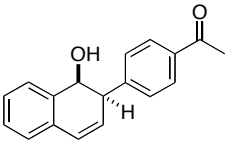
Table 2.4 Pd-Catalyzed Ring Opening Reaction with Aryl and Vinyl Halides[a]

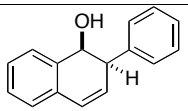
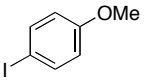
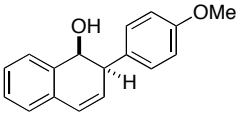
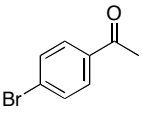
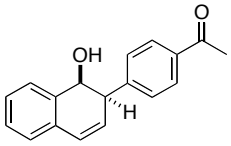


2.7a: R' = OMe
2.7b: R' = H

2.32a-2.44a

Entry	Oxabicycle	RX	Temp (°C)[b]	Time (h)	Product	Yield (%)[c]
1	**2.7a**		rt	2.5	 **2.32a**	95
2	**2.7a**		rt	4	 **2.33a**	90
3	**2.7a**		rt	2.5	 **2.34a**	92
4	**2.7a**		35	1.5	 **2.35a**	95
5	**2.7a**		35	2.5	 **2.36a**	83
6	**2.7a**		35	25	 **2.37a**	94

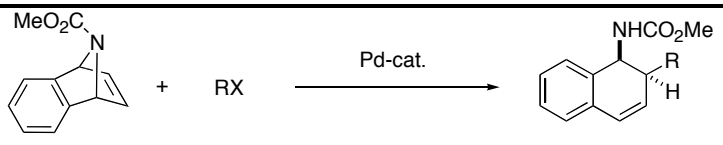
Entry	Oxabicycle	RX	Temp (°C)[b]	Time (h)	Product	Yield (%)[c]
7	**2.7a**		60	20	 **2.38a**	71
8[e]	**2.7a**		70	1.5	 **2.39a**	73
9[d]	**2.7a**		55	15	 **2.32a**	71
10[d]	**2.7a**		45	12	 **2.33a**	73
11[d]	**2.7a**		60	26	 **2.40a**	90
12[d]	**2.7a**		60	14	 **2.35a**	73
13[e]	**2.7a**		75	3.5	 **2.41a**	62
14	**2.7b**		rt	2	 **2.42a**	97

Entry	Oxabicycle	RX	Temp (°C)[b]	Time (h)	Product	Yield (%)[c]
15	**2.7b**		35	2	 **2.43a**	95
16	**2.7b**		35	2.5	 **2.44a**	97
17	**2.7b**		50	6	 **2.42a**	70

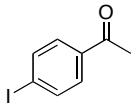
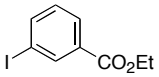
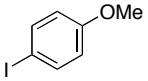
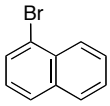
[a]Conditions: 0.05 M of **2.7a** or **2.7b** in DMF, RX (1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (11 mol%), PMP (0.5 equiv), Zn (10 equiv). [b]Oil bath temperature. [c]Isolated yield of product after chromatography. [d]$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%). [e]$Pd(OAc)_2$ (15 mol%), PPh_3 (30 mol%).

We also extended the methodology to a 7-azabenzonorbornadiene **2.7c**. Under the similar conditions that had been developed for the ring opening of **2.7a** and **2.7b**, aryl iodides bearing electron-donating and -withdrawing groups as well as simple aryl bromides could be used in these cross-couplings to give the desired *cis*-2-substitued-(1,2-dihydro-1-naphthyl)carbamates in excellent yields (Table 2.5). For these reactions, no dehydroamination to give naphthalene by-products was observed.

Table 2.5 Pd-Catalyzed Ring Opening of **2.7c** with Aryl Halides[a]



2.7c **2.45-2.49**

Entry	RX	Temp (°C)[b]	Time (h)	Product	Yield (%)[c]
1		rt	12	**2.45**	91
2		rt	6	**2.46**	96
3		40	7	**2.47**	92
4		40	7	**2.48**	96
5[d]		65	12	**2.49**	92

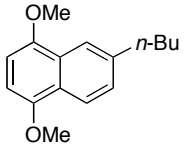
[a]Conditions: 0.05 M of **2.7c** in DMF, RX (1.2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (11 mol%), PMP (0.5 equiv), Zn (10 equiv). [b]Oil bath temperature. [c]Isolated yield of product after chromatography. [d]$Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%).

2.4 RING OPENING OF OXABENZONORBORNADIENES WITH LITHIUM REAGENTS

Ring opening of oxabenzonorbornadienes with butyllithiums (*n*-BuLi, *t*-BuLi) was first reported by Nelson in 1971.[72] The reaction proceeded at room temperature in Et_2O solution in the absence of transition metal catalysts. However, the purification of final product required several sublimations or distillations. We changed the solvent from Et_2O to THF, and found that ring opening of oxabenzonorbornadienes with alkyllithiums in the presence of TMEDA occurred at low temperatures. Under these conditions, purification of products with chromatography on silica gel was relatively easy. Treatment

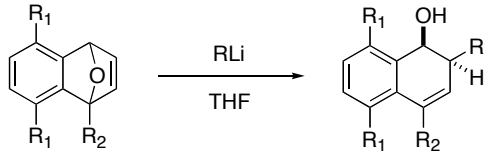
of **2.7a** with *n*-BuLi (5 equiv) in the presence of TMEDA[119] (2 equiv) at -78 ºC provided **2.51a** in excellent yield (Table 2.6, Entry 1). Since the ^{1}H and ^{13}C NMR spectra of compound **2.51a** are consistent with those reported previously,[120] it is believed that alkylative ring opening reaction proceeds through *exo* attack to give the *cis* product. In the absence of TMEDA, the reaction proceeded relatively slowly. Raising the temperature to 0 ºC resulted in the isolation of variable amounts of the naphthalene **2.50** as a by-product (Figure 2.4). Under the similar conditions as Entry 1, addition of *n*-BuLi to cycloadduct **2.7d** bearing a methyl group at the bridgehead gave **2.52a** in excellent yield (Entry 2). Ring opening of **2.7a** with BnLi in the presence of TMEDA in toluene at 0 ºC provided **2.53a** in good yield (Entry 3). The reaction was finished within 3 min, but increasing the reaction time tended to increase the amount of naphthalene by-product. Ring opening of **2.7a**-**b** with *t*-BuLi, which is a better nucleophile than *n*-BuLi and BnLi, proceeded at -78 ºC to provide **2.54a**-**2.55b** in excellent yields, and these reactions did not require TMEDA (Entry 4-5).

Figure 2.4



2.50

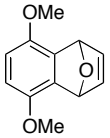
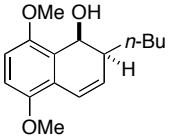
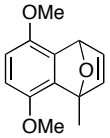
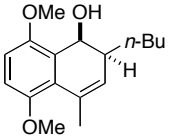
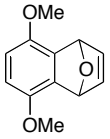
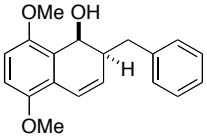
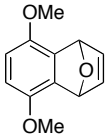
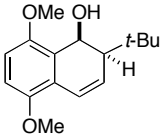
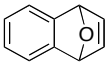
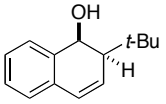
Table 2.6 Ring Opening of Oxabenzonorbornadienens with Lithium Reagents[a]



R_1 = OMe or H
R_2 = Me or H

2.7a-d

2.51a-2.55a

Entry	Oxabicycle	RLi	Product	Yield(%)[b]
1[c]	 **2.7a**	*n*-BuLi	 **2.51a**	98
2[c]	 **2.7d**	*n*-BuLi	 **2.52a**	98
3[c,d]	 **2.7a**	BnLi	 **2.53a**	81
4	 **2.7a**	*t*-BuLi	 **2.54a**	98
5	 **2.7b**	*t*-BuLi	 **2.55a**	87

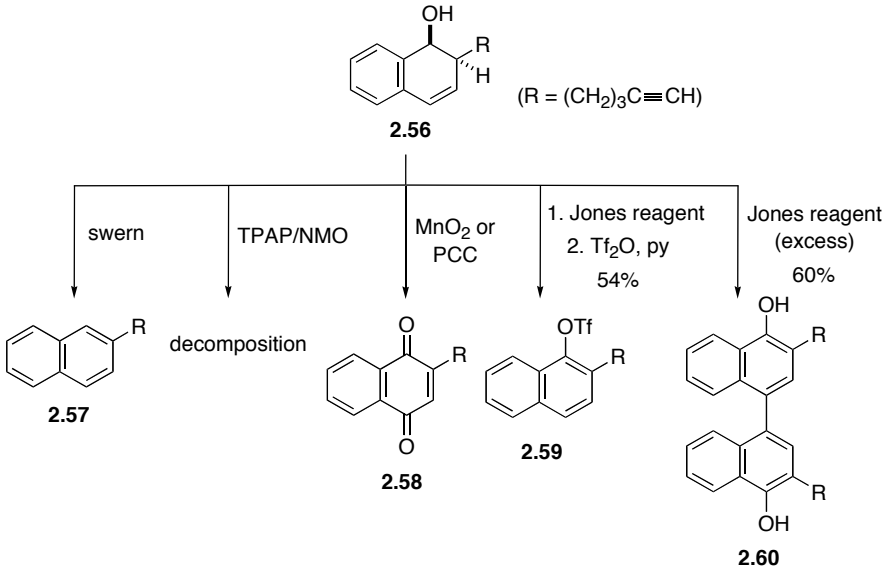
[a]Conditions: 0.1M of **2.7a**-**d**, RLi (5 equiv), -78 ºC.

[b]Isolated yield of product after chromatography. [c]TMEDA (2 equiv). [d]0 ºC in toluene.

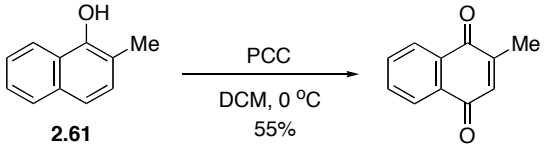
2.5 OXIDATION OF 2-SUBSTITUTED-1,2-DIHYDRONAPHTHOLS

After establishing the generality of the cross-couplings of the 7-oxabenzonorbornadienes **2.7a** and **2.7b**, the next objective was to develop conditions for affecting the oxidation of the intermediate dihydronaphthols to give naphthols. However, oxidation of 1,2-dihydronaphthols to the 1-naphthols was known to be problematic.[105] For example, Fillion reported that oxidation of dihydronaphthol **2.56** with the Swern protocol or TPAP/NMO led to the formation of naphthalene **2.57** via elimination of the labile secondary benzylic alcohol, or to decomposition, respectively (Scheme 2.8).[105] Furthermore, oxidation of **2.56** with MnO_2 or PCC gave naphthoquinone **2.58**. Unexpectedly, the highly acidic Jones reagent in acetone oxidized **2.56** to the corresponding 1-naphthol, which was subsequently protected as a triflate **2.59**. However, the reaction was difficult to reproduce on gram-scale. Using an excess of Jones reagent for the oxidation of **2.56** led to the naphthol dimmer **2.60**.

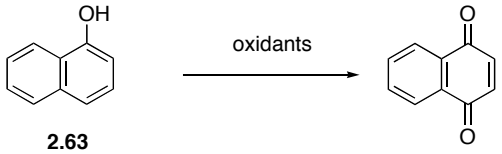
Scheme 2.8



Several reports showed that 1-naphthol was not stable toward oxidants, and oxidation usually occurred to give 1,4-naphthoquinones. For example, treatment of 1-naphthol **2.61** with PCC led to the formation of quinone **2.62** (Eq 2.2).[105] Moreover, oxidation of **2.63** with H_2O_2/CH_3ReO_3, HIO_3/K10 montmorillonite, aqua(hydroxy)(aryl)iodonium complexes, $MnCl_2/CoCl_2/O_2$, $CuCl/O_2$, $PhI(OTf)_2$ or Fremy's salt provided quinone **2.64** (Eq 2.3).[121]



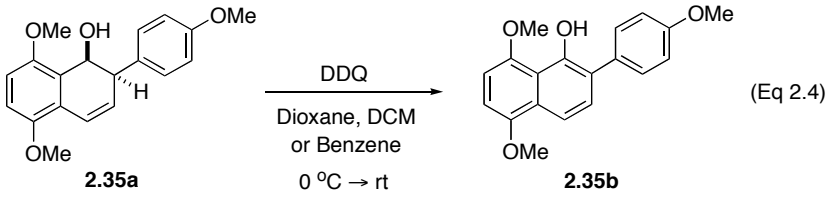
2.61 **2.62** (Eq 2.2)



2.63 **2.64** (Eq 2.3)

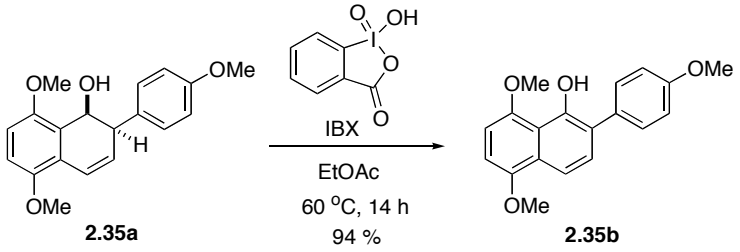
We mentioned in Chapter 2.1 that glycal substituted *cis*-1,2-dihydronaphthols could be oxidized to the corresponding *C*-aryl glycosides using recrystallized DDQ.[90a] However, oxidation of **2.35a** under these conditions provided only trace amounts of the desired 2-aryl-1-naphthol **2.35b**, and little starting **2.35a** was recovered (Eq 2.4). A variety of oxidants were screened to effect this transformation, but the naphthol **2.35b** was invariably isolated in poor yield together with the dehydration product and/or recovered starting material as well as several unidentified products. For example, oxidation of **2.35a** with Dess-Martin periodinane, PCC, Swern reagent, $Pd(OAc)_2$/pyridine/O_2/toluene, [122] $Pd(OAc)_2/NaHCO_3/O_2$/DMSO, [123] $Pd(PPh_3)_4$/PhBr/ DMF/K_2CO_3 or NaH,[124] or IBX/H_2O/acetone/β-cyclodextrin[125] provided naphthol **2.35b** in less than 30% yield; simple dehydration was the major reaction in all of these experiments. Other oxidants including TPAP, DMSO/NEt_3/py·SO_3, MnO_2, *p*-chloranil,

Pd(nbd)Cl_2/sparteine/O_2,[126] NCS/DMS/Et_3N, and DMDO[127] gave only trace amounts of **2.35b** together with several unidentified products and/or recovered starting material **2.35a**.



(Eq 2.4)

Gratifyingly, we eventually discovered that IBX,[128] 1-hydroxy-1,2-benziodoxol-3(*1H*)-one 1-oxide (2-iodoxybenzoic acid), was an effective oxidant to promote this transformation. Oxidation of **2.35a** with 3 equiv of IBX, in EtOAc at 60 °C for 14 h provided naphthol **2.35b** in 94% yield (Eq 2.5). A similar yield was also obtained when reaction proceeded at 80 °C for 3 h. Acetone was also found to be a suitable solvent. Treatment of **2.35a** with IBX (3 equiv) in acetone at 40 °C for 14 h provided naphthol **2.35b** in 80% yield. DMSO, which is frequently used as solvent in IBX oxidations, [129] was not satisfactory because the naphthol **2.35b** underwent more rapid decomposition, presumably by oxidation, in DMSO than in the other solvents. For example, treatment of **2.35b** with IBX (3 equiv) in DMSO at room temperature for two hours only recovered less than 10% of **2.35b** along with several unidentified products.



(Eq 2.5)

Having discovered that IBX was an effective oxidant for converting **2.35a** into **2.35b**, we then employed it to oxidize a variety of substituted dihydronaphthols to give

the corresponding 1-naphthols, and these results are summarized in Table 2.7. These oxidations generally provided good to excellent yields with only small amounts of the corresponding naphthalenes being observed in the crude reaction mixtures. Since the product 1-naphthols were found to be somewhat unstable toward excess IBX, the yields in these oxidations were found to depend critically upon temperatures, reaction times, solvents, and the number of equivalents of IBX used. Some optimization was thus necessary to improve the yield for oxidizing a given dihydronaphthol. For example, the oxidations of **2.32a** and **2.36a** in EtOAc to give **2.32b** and **2.36b** proceeded in 51% and 60% yields, respectively, at 80 °C. The corresponding yields were improved to 88% and 80% when the reactions were performed at 60 °C. Although ethyl acetate was frequently the solvent of choice, oxidations of **2.33a** and **2.34a** provided better yields in acetone because **2.33b** and **2.34b** appeared to be less stable toward IBX in EtOAc. It is worth noting that this oxidation is not limited to the production of 2-aryl-1-naphthols. IBX can also be used to oxidize 2-alkyl-1,2-dihydronaphthols and 2-vinyl-1,2-dihydronaphthols to give the corresponding 2-substituted naphthols as exemplified by the oxidations of **2.41a**, **2.51a** and **2.53a**-**2.55a**.

However, our preliminary experiments showed that the *cis*-2-substitued-(1,2-dihydro-1-naphthyl)carbamates were quiet stable toward IBX. For example, treatment of **2.45** with IBX (3 equiv) in EtOAc at 80 °C only recovered starting material **2.45** (Scheme 2.9). Changing the solvent to acetone or DMSO and performing reaction at 80 °C led to the similar results. Eventually, the use of THF led to the naphthylamide **2.65**; however, the oxidation was slow and provided recovered **2.45** along with several unidentified products.

Scheme 2.9

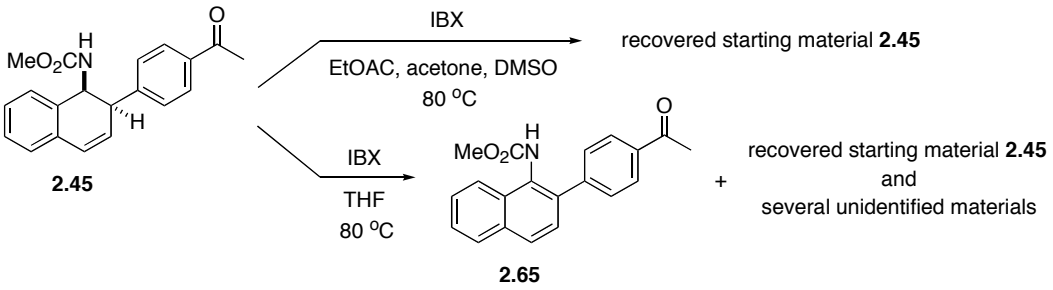
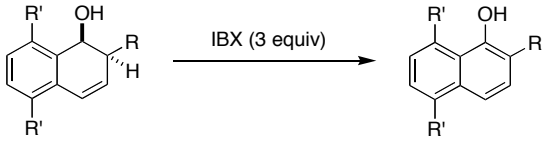
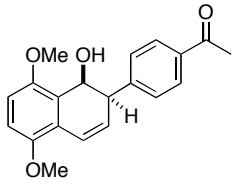
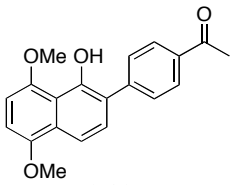
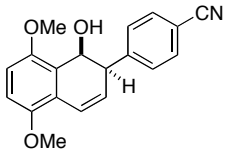
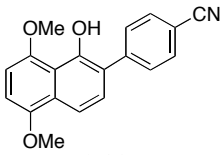
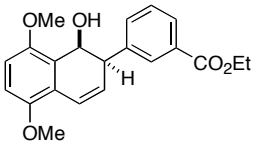
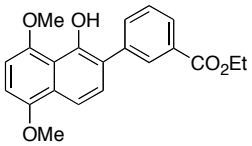
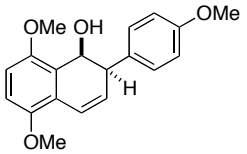
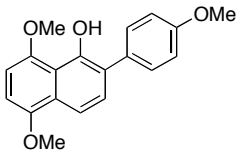
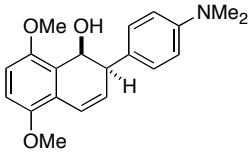
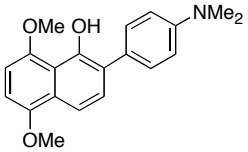
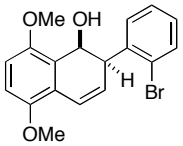
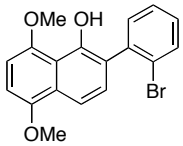
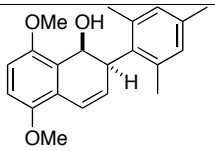
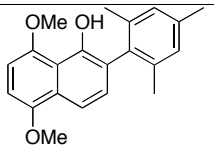
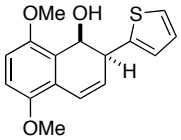
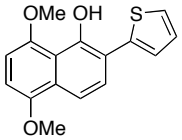
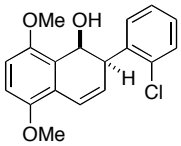
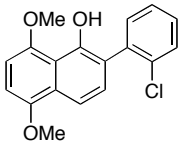
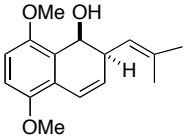
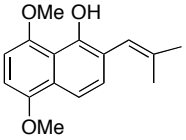
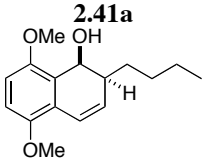
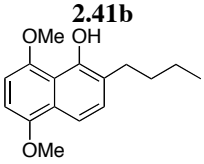
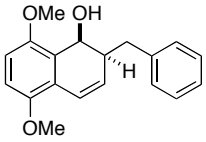
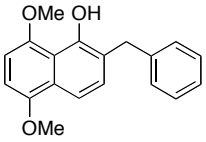
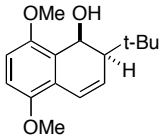
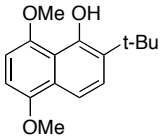
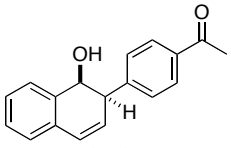
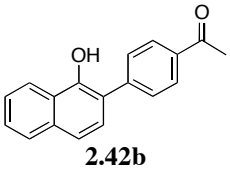
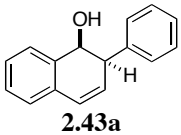
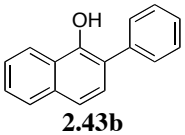
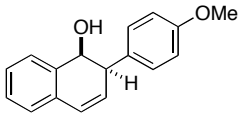
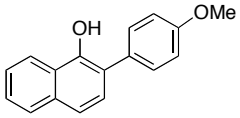
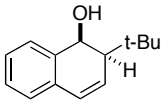
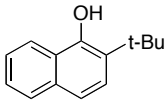

H
MeO2CN
O
H
2.45
IBX
EtOAC, acetone, DMSO
80 °C
recovered starting material 2.45
IBX
THF
80 °C
H
MeO2CN
O
2.65
+
recovered starting material 2.45
and
several unidentified materials

Table 2.7 Oxidation of 2-Substituted-1,2-Dihydro-1-Naphthols with IBX



Entry	Alcohol	Solvent	Temp (°C)[a] /Time (h)	Product	Yield (%)[b]
1	 **2.32a**	EtOAc	60/14	 **2.32b**	88
2	 **2.33a**	acetone	40/20	 **2.33b**	76
3	 **2.34a**	acetone	40/20	 **2.34b**	81
4	 **2.35a**	EtOAc	60/14	 **2.35b**	94
5	 **2.36a**	EtOAc	60/5	 **2.36b**	80
6	 **2.37a**	EtOAc	60/16	 **2.37b**	92

Entry	Alcohol	Solvent	Temp (°C)[a] /Time (h)	Product	Yield (%)[b]
7	 **2.38a**	EtOAc	80/3	 **2.38b**	95
8[c]	 **2.39a**	EtOAc	80/3	 **2.39b**	81
9	 **2.40a**	EtOAc	60/24	 **2.40b**	84
10	 **2.41a**	EtOAc	80/1.5	 **2.41b**	67
11	 **2.51a**	EtOAc	80/3.5	 **2.51b**	85
12	 **2.53a**	EtOAc	80/3	 **2.53b**	91
13	 **2.54a**	EtOAc	80/3	 **2.54b**	91
14[d]	 **2.42a**	THF	40/3	 **2.42b**	46
15[d]	 **2.43a**	THF	40/3	 **2.43b**	63

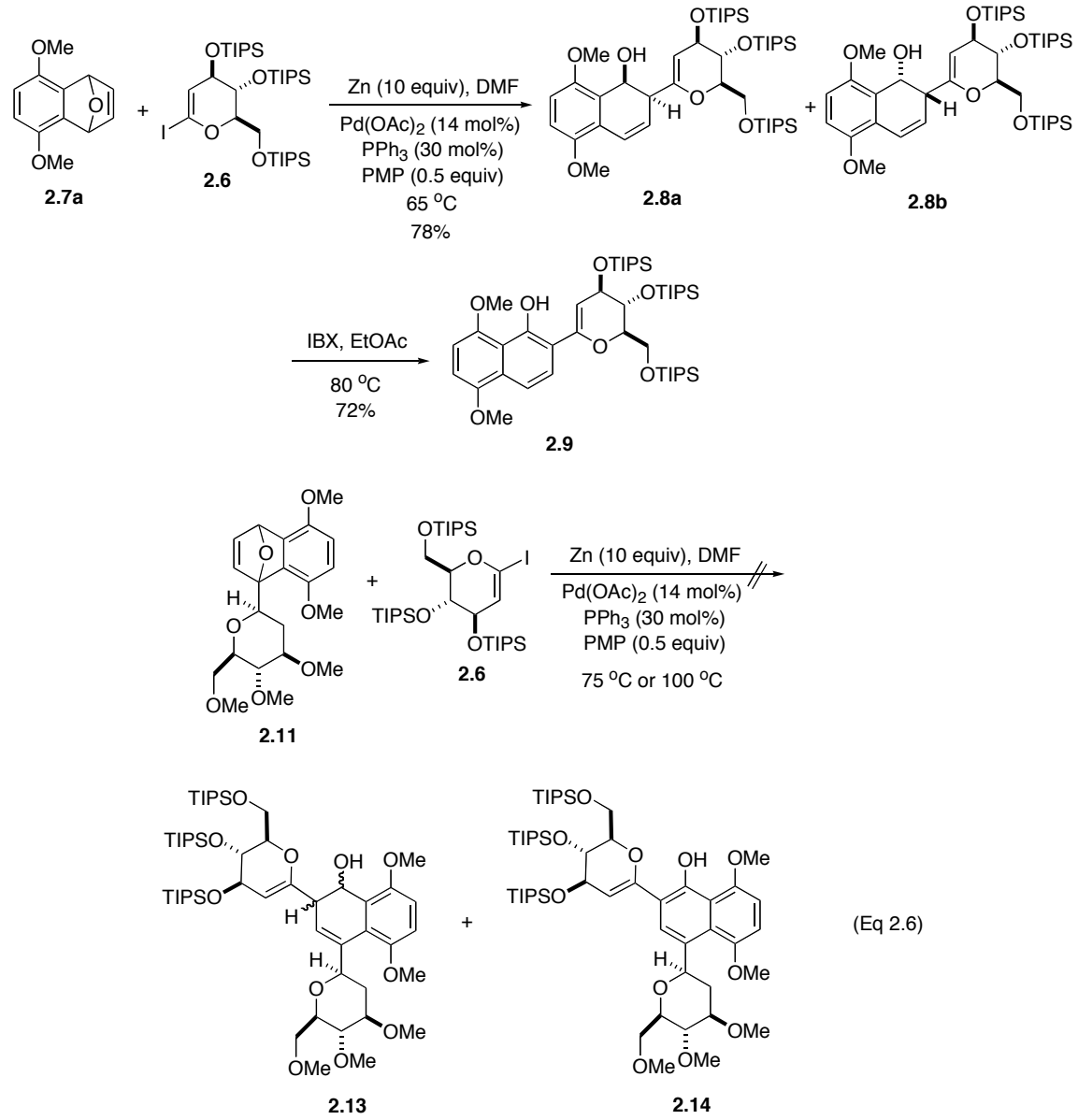
Entry	Alcohol	Solvent	Temp (°C)[a] /Time (h)	Product	Yield (%)[b]
16[d]	 **2.44a**	THF	40/3.5	 **2.44b**	52
17[d]	 **2.55a**	THF	50/2.5	 **2.55b**	80

[a]Oil bath temperature. [b]Isolated yield of product after chromatography. [c]IBX (1.5 eq). [d]IBX (2 eq).

2.6 APPLICATIONS TO SYNTHESIS OF *C*-ARYL GLYCOSIDES

In connection with our ongoing efforts directed toward the synthesis of Group II *C*-aryl glycosides, we applied these new ring opening and oxidation protocols to an improved route to **2.9**. Thus, the palladium-catalyzed ring opening of oxabenzonorbornadiene **2.7a** with glycal iodide **2.6** provided a mixture (4:1) of diastereomeric *cis*-dihydronaphthols **2.8a** and **2.8b** in 78% yield (Scheme 2.10); the relative stereochemistry of the major isomer was not established. Subsequent oxidation of this mixture with IBX cleanly provided *C*-aryl glycoside **2.9** in 72% yield with no dehydration of the intermediate dihydronaphthols **2.8a** and **2.8b** being observed. Having demonstrated that representative Group II *C*-aryl glycosides **2.9** were accessible, it remained to prepare a more challenging Group III *C*-aryl glycosides. Unfortunately, palladium-catalyzed ring opening of **2.11** with glycal iodide **2.6** at 75 °C or 100 °C provided several unidentified materials rather than the corresponding dihydronaphthols **2.66** or naphthol **2.14** (Eq 2.6).

Scheme 2.10


OMe
OMe
2.7a
OTIPS
OTIPS
I
O
OTIPS
2.6
Zn (10 equiv), DMF
Pd(OAc)2 (14 mol%)
PPh3 (30 mol%)
PMP (0.5 equiv)
65 °C
78%
OMe OH
OTIPS
OTIPS
OTIPS
2.8a
2.8b
IBX, EtOAc
80 °C
72%
2.9
TIPSO
TIPSO
TIPSO
2.11
Zn (10 equiv), DMF
Pd(OAc)2 (14 mol%)
PPh3 (30 mol%)
PMP (0.5 equiv)
75 °C or 100 °C
2.13
2.14
(Eq 2.6)

2.7 CONCLUSION

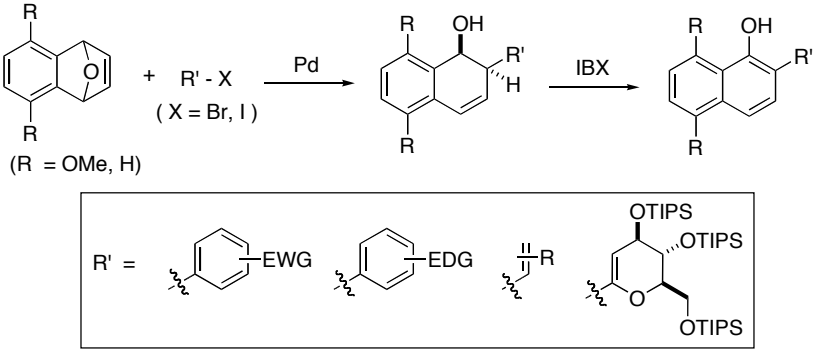
A palladium-catalyzed tandem ring opening/oxidation reaction was developed that involved the palladium-catalyzed ring opening of oxabenzonorbornadienes with aryl iodides followed by oxidation *in situ* to give 2-aryl-1-naphthols (see Scheme 2.1). However, application of tandem couplings for the synthesis of *C*-aryl glycosides did not provide promising results. (see Table 2.2 and Eq 2.1). We then decided to adopt a two-step procedure toward the synthesis of *C*-aryl glycosides *via* ring opening of oxabenzonorbornadienes with glucal iodides and subsequent oxidation of the resultant dihydronaphthols.

In the past, the palladium-catalyzed ring opening of oxabenzonorbornadienes with electron-rich aryl iodides provided *cis*-2-substituted-1,2-dihydro-1-naphthols in good yields.67 However, transformations involving electron-deficient aryl and vinyl iodides gave primarily naphthalenes, and reactions with aryl and vinyl bromides typically proceeded in low yield. Under the mild conditions we discovered [$Pd(OAc)_2$, PPh_3, Zn, and PMP in dry DMF], the palladium-catalyzed ring opening of oxabenzonorbornadienes proceeded with a variety of organic halides to give the corresponding *cis*-2-substituted-1,2-dihydro-1-naphthols in good to excellent yields (Scheme 2.11). These organic halides included aryl iodides and bromides bearing both electron-withdrawing and -donating groups, vinyl bromides and glycal iodides. Similarly, a 7-azabenzonorbornadiene substituted with an electron withdrawing group on the nitrogen atom underwent facile ring opening reaction with aryl iodides or bromides to provide *cis*-2-substitued-(1,2-dihydro-1-naphthyl)carbamates in excellent yields. Under these conditions, the formation of naphthalene by-products, which are commonly observed by Cheng,[67] is suppressed.

Oxidation of dihydronaphthols to naphthols usually accompanied the formation of naphthalene, quinone and aromatic dimer by-products.[90a-c,e,f,105] After examining numerous oxidants, we discovered that oxidation of the intermediate *cis*-2-substituted-1,2-dihydro-1-naphthols using IBX yielded the corresponding 2-substituted-1-naphthols in good to excellent yields (Scheme 2.11).

We then applied the palladium-catalyzed ring opening reactions and IBX oxidations for the synthesis of *C*-aryl glycosides. The palladium-catalyzed ring opening of oxabenzonorbornadienes with glucal iodide **2.6** and subsequent oxidation of the resultant dihydronaphthols with IBX led to a Group II *C*-aryl glycoside model **2.9** in a superior overall yield. However, using this protocol to prepare Group III *C*-aryl glycoside model **2.14** did not provide fruitful results.

Scheme 2.11

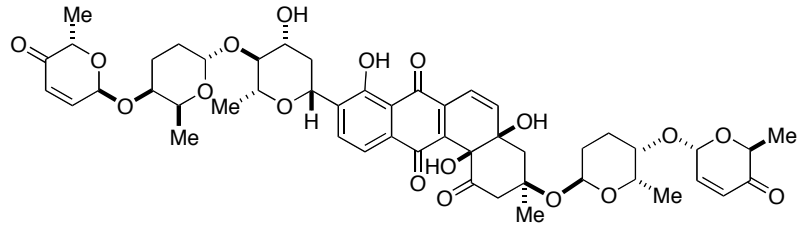


Chapter 3. Previous Total Synthesis of Vineomycinone B_2 Methyl Ester

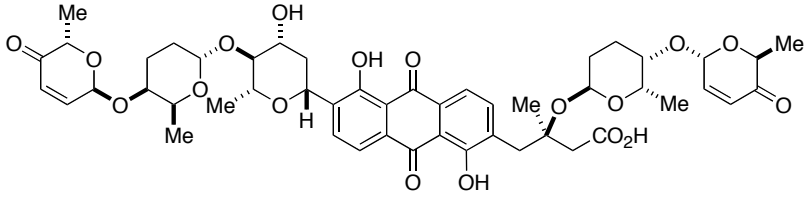
3.1 Biological Activity and Structure of Vineomycinone B_2 Methyl Ester

The vineomycins (A_1, A_2, B_1 and B_2) comprise a group of antibiotics that were isolated from a culture of *Streptomyces matensis vineus* and found to be active against Gram-positive bacteria and sarcoma-180 solid tumors in mice.[130] The structure of vineomycins A_1 and B_2 have been reported and are shown in Figure 3.1. Vineomycin A_1 (**3.1**) was found to be identical with a Streptomyces metabolite, P-1894B, which is a potent inhibitor of prolyl hydroxylase (IC_{50} = 2.2 μM).[131] Prolyl hydroxylase is an oxygenase that catalyzes the hydroxylation of specific prolyl residues in the peptide precursor of collagen to 4-hydroxyproline. Moreover, prolyl hydroxylase is one of the key enzymes in collagen biosynthesis, and its activity is enhanced in tissues of pathological fibrosis.[132] Vineomycin A_1 is a suitable treatment for hypertrophic scar tissue and keloid in vivo studies.[133] Vineomycin B_2 (**3.2**) has been used as a biochemical tool as a collagen prolyl hydroxylase inhibitor.[134] The first biosynthestic study of the vineomycin family was carried out by Õmura *et al.*[135] Feeding experiments with single and double [^{13}C] labeled acetate elucidated that the entire tetracyclic ring system of vineomycinone A_1 (**3.1**) as well as the carbon skeleton of vineomycinone B_2 (**3.2**) was derived from a single decaketide chain.[136]

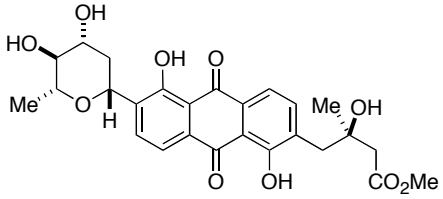
Figure 3.1



Vineomycin A_1 (**3.1**)



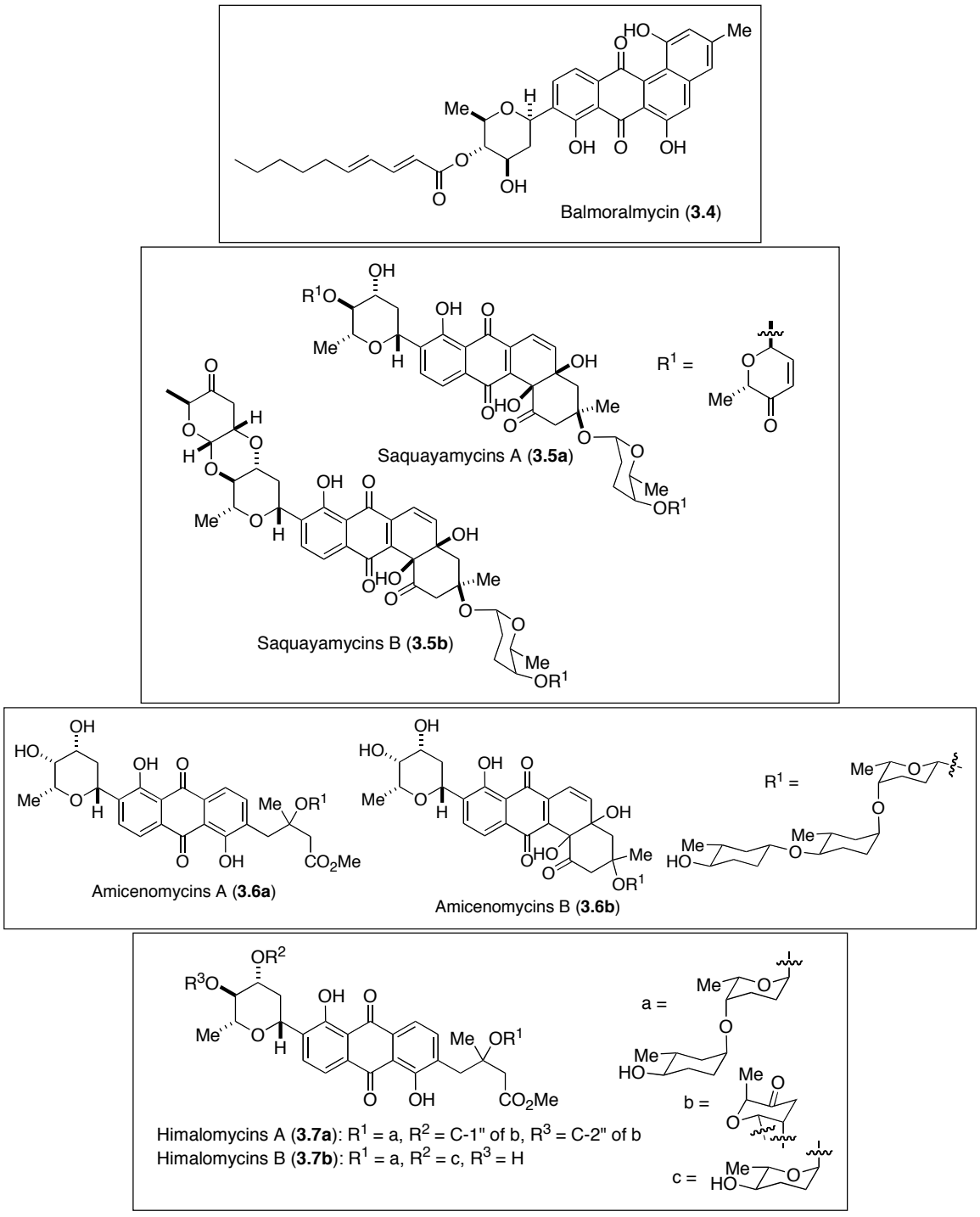
Vineomycin B_2 (**3.2**)



Vineomycinone B_2 methyl ester (**3.3**)

Several natural products, which are structurally similar to the vineomycin family, have shown significant biological activities. For example, balmoralmycin (**3.4a**-**b**) is an inhibitor of protein kinase C-α with an IC_{50} value of 50 μM (Fig 3.2).[137] Saquaymycins A and B (**3.5a**-**b**) are active against L1210, A549 and HT29 tumor cells.[138] Amicenomycins A and B (**3.6a**-**b**) exhibit antimicrobial activities, and the acute toxicities (LD_{50}, ip) in mice are estimated to be >100.0 mg/kg and 17.5-35 mg/kg, respectively.[139] Himalomycin A and B (**3.7a**-**b**) have strong antibacterial activity.[140]

Figure 3.2

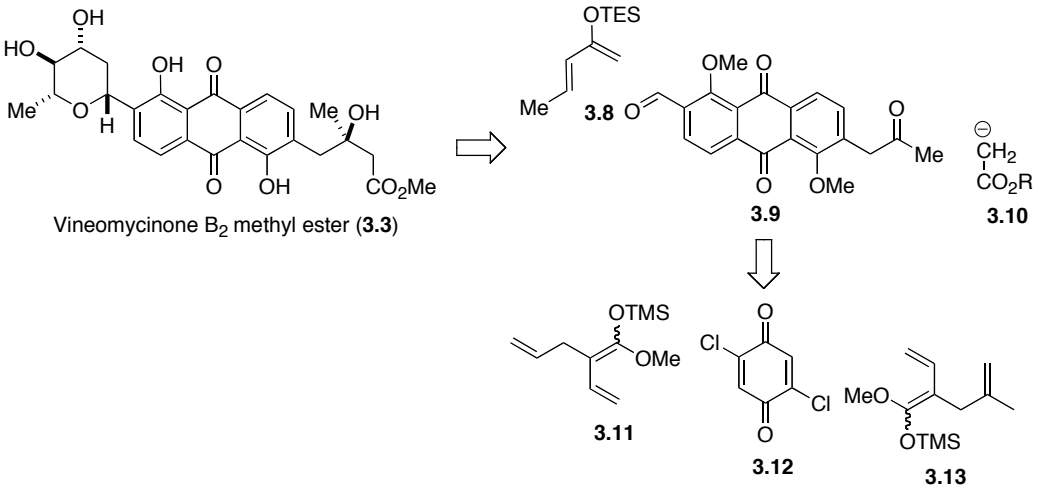

Balmoralmycin (3.4)
Saquayamycins A (3.5a)
Saquayamycins B (3.5b)
Amicenomycins A (3.6a)
Amicenomycins B (3.6b)
Himalomycins A (3.7a): R1 = a, R2 = C-1" of b, R3 = C-2" of b
Himalomycins B (3.7b): R1 = a, R2 = c, R3 = H

Treatment of both vineomycin A_1 and vineomycin B_2 with 5% HCl in MeOH at 90 °C provided the degradation product vineomycinone B_2 methyl ester (**3.3**), which was also generated from the acid-catalyzed methanolysis of aquayamycin.[130b, 141] Vineomycinone B_2 methyl ester (**3.3**), which bears an olivose residue appended to one ring of the anthrarufin core, is a representative member of the *C*-aryl glycoside family of natural products.[142] A 3(*R*)-hydroxyisovaleryl side chain is attached to the opposite side of the core making vineomycinone B_2 methyl ester a fascinating target. Indeed, the structure feature of **3.3** coupled with the unique biological activity of the vineomycin family has rendered vineomycinone B_2 methyl ester the object of a number of investigations. Until now, four total syntheses of vineomycinone B_2 methyl ester have been reported. [143]

3.2 DANISHEFSKY'S TOTAL SYNTHESIS OF VINEOMYCINONE B_2 METHYL ESTER

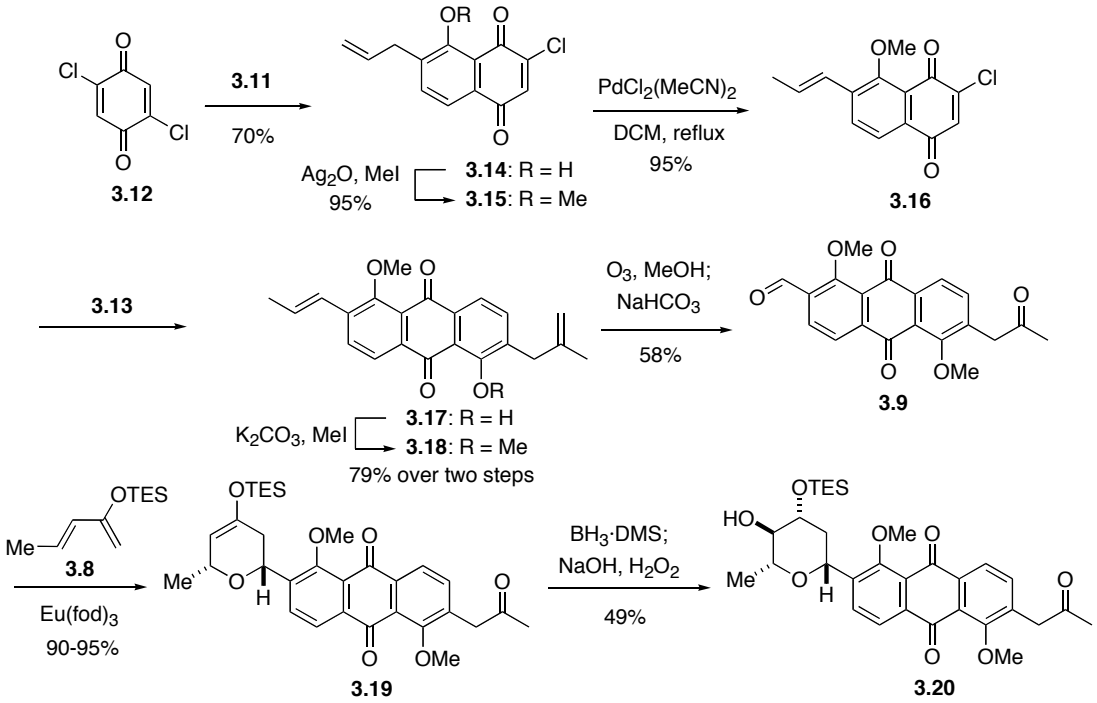
The first total synthesis of vineomycinone B_2 methyl ester was reported by Danishefsky in 1984.[143a-b] His approach relied on three Diels-Alder reactions to construct the *C*-glycosyl and anthrarufin frameworks. The *C*-glycoside residue was derived from a hetero Diels-Alder reaction between siloxy diene **3.8** and the aldehyde group of **3.9** (Scheme 3.1). The methyl ester moiety would arise from a Reformatsky coupling of a ketone with an acetate anion **3.10** bearing a chiral auxiliary. Substituted ketoaldehyde **3.9** was assembled by sequential Diels-Alder reactions of quinone **3.12** with siloxy dienes **3.11** and **3.13**.

Scheme 3.1



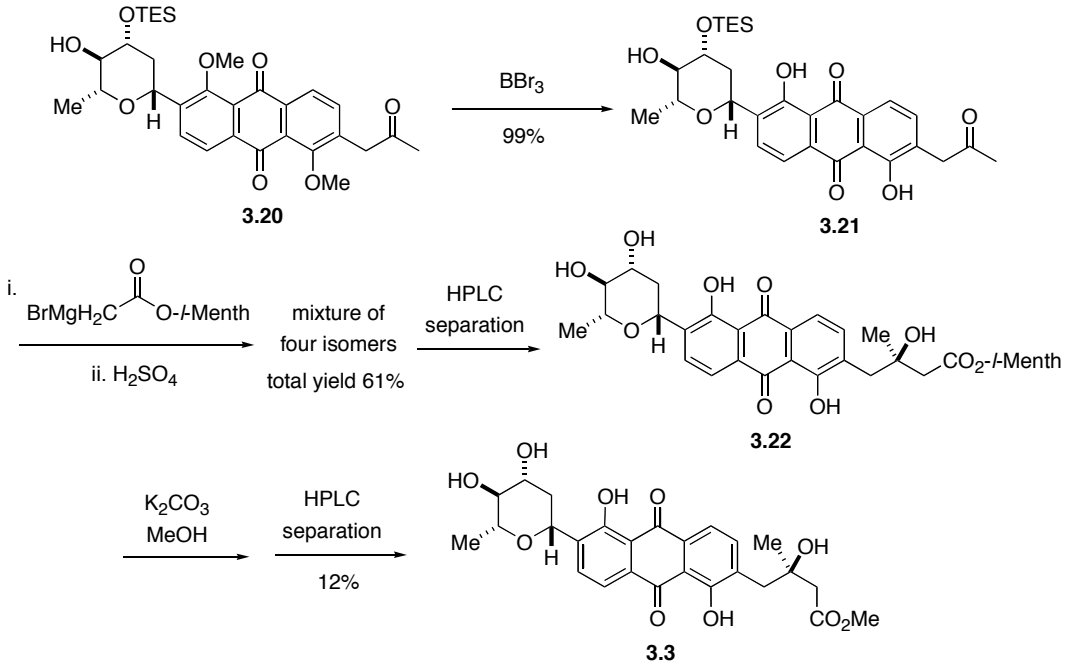
Preparation of ketoaldehyde **3.9** commenced with the cycloaddition of quinone **3.12** with diene **3.11** to afford chlorojuglone **3.14**, which was transformed to methyl ether **3.15** by *O*-methylation (Scheme 3.2).[143a-b] The palladium-catalyzed isomerization of the allyl functionality provided **3.16** that contains the required propenyl group.[144] A second cycloaddition of **3.16** with diene **3.13** followed by methylation gave anthraquinone **3.18**. Ozonolysis of **3.18** afforded the desired ketoaldehyde **3.9**. Construction of the *C*-glycoside was launched by Diels-Alder cycloaddition of ketoaldehyde **3.9** with diene **3.8** in the presence of catalytic $Eu(fod)_3$ to provide *endo* product **3.19** in excellent yield.[145,146] Hydroboration of **3.19** with borane dimethylsulfide followed by oxidative work-up gave racemic *C*-glycosyl anthraquinone **3.20**.

Scheme 3.2



The final task of the synthesis required removal of the protecting groups and introduction of the methyl ester moiety. Demethylation of **3.20** with boron tribromide in methylene chloride at -78 ºC provided anthrarufin **3.21** (Scheme 3.3). At this step, the triethylsilyl group was unaffected under these conditions. Treatment of **3.21** with the bromomagnesium salt of *l*-menthyl ester followed by an acidic workup gave a mixture of four isomers. The *l*-menthyl ester **3.22** was obtained as a single stereoisomer *via* separation by HPLC, but the yield was not provided. Transesterification of **3.22** with potassium carbonate in methanol and subsequent separation by HPLC afforded synthetic vineomycinone B_2 methyl ester.

Scheme 3.3



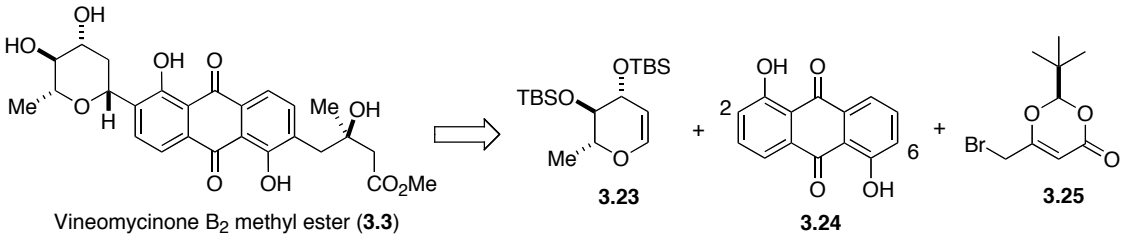
The application of three Diels-Alder cycloadditions with simple siloxydienes generated the olivose and anthrarufin skeletons in good yields with excellent regioselectivites. Using these cycloadditions as the key steps led to a highly convergent total synthesis of vineomycinone B_2 methyl ester. The synthesis was completed in a total of 15 steps in 0.05% yield from commercially available materials. The longest linear sequence required 12 steps and proceeded in 0.1% yield. Althoug the synthesis is relative short, the overall yield is not promising. The Reformatsky-like reaction using bromomagnesium salt of *l*-menthyl ester and transesterification of **3.22** with potassium carbonate provided products in low yields and required purification by HPLC.

3.3 TIUS' TOTAL SYNTHESIS OF VINEOMYCINONE B_2 METHYL ESTER

Vineomycinone B_2 methyl ester (**3.3**) possesses the *C*-glycosyl bond to the olivose derivative and an alkyl side chain bearing a stereogenic center on the opposite

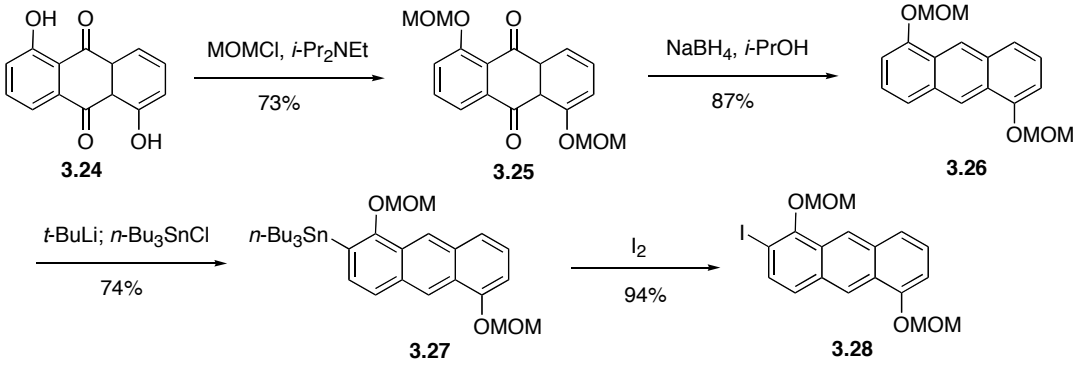
side of the molecule. Tius envisioned that vineomycinone B_2 was derived from the assembly of three subunits: an anthrarufin **3.24**, olivose **3.23** and a mevalonate synthron **3.25** (Scheme 3.4).[143c-d] Each of the subunits was prepared efficiently from commercially available materials. The synthetic challenges were the formation of carbon-carbon bonds at C2 and C6 of anthrarufin **3.24**, controlling the stereochemistry of the *C*-glycosylation, and generation of an asymmetric tertiary alcohol.

Scheme 3.4



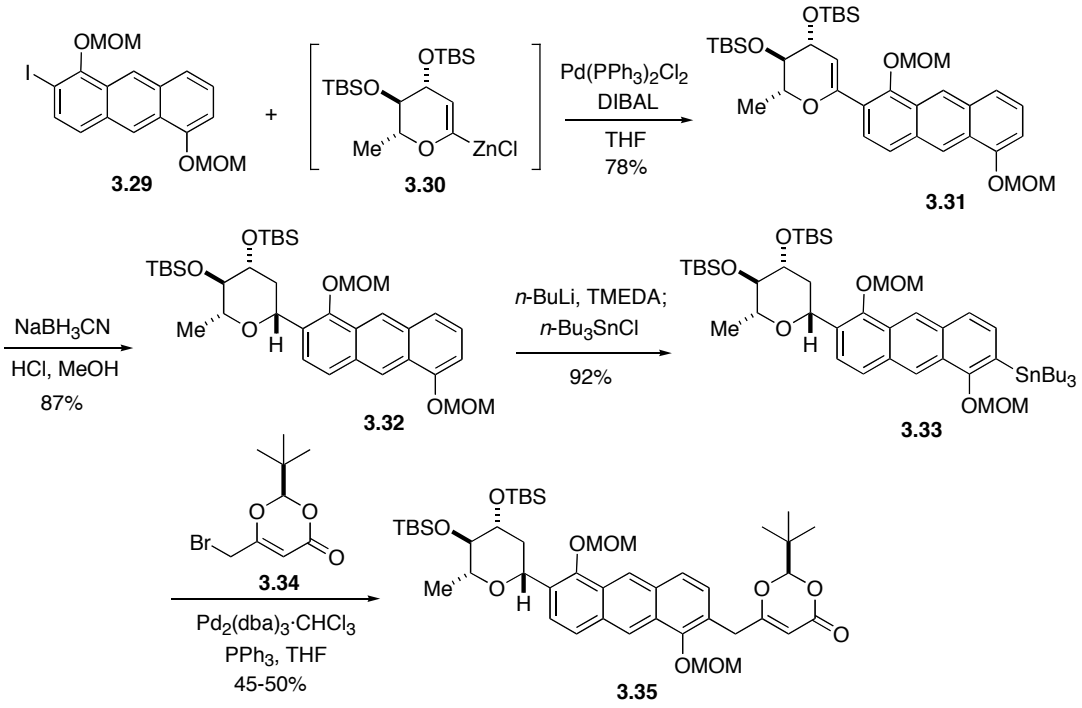
The synthesis commenced with commercially available anthrarufin **3.24**, which was protected as a MOM ether followed by reduction with $NaBH_4$ to give anthracene **3.26** (Scheme 3.5). MOM group directed deprotonation in the presence of *tert*-BuLi followed by trapping of the resultant anion with *n*-Bu_3SnCl gave stannane **3.27**. Iodination of **3.27** with freshly sublimed iodine produced iodoanthracene **3.28**.

Scheme 3.5



Attachment of the olivose subunit to the anthracene framework then proceeded *via* a Nigishi coupling[147] of iodoanthracene **3.29** with the glucal zinc **3.30** to give glycosyl anthracene **3.31** (Scheme 3.6). Reduction of **3.31** with $NaBH_3CN$ in methanolic HCl furnished anthracene **3.32** as a single diastereomer. The high regioselectivity was presumably attributed to the stereoelectronic effect. Selective lithiation of **3.32** with *n*-BuLi in the presence of TMEDA and subsequent quenching with *n*-Bu_3SnCl afforded stannane **3.33**. Palladium-catalyzed coupling[148] of allyl bromide **3.34** with **3.33** gave anthracene **3.35** in 45-50% yield.

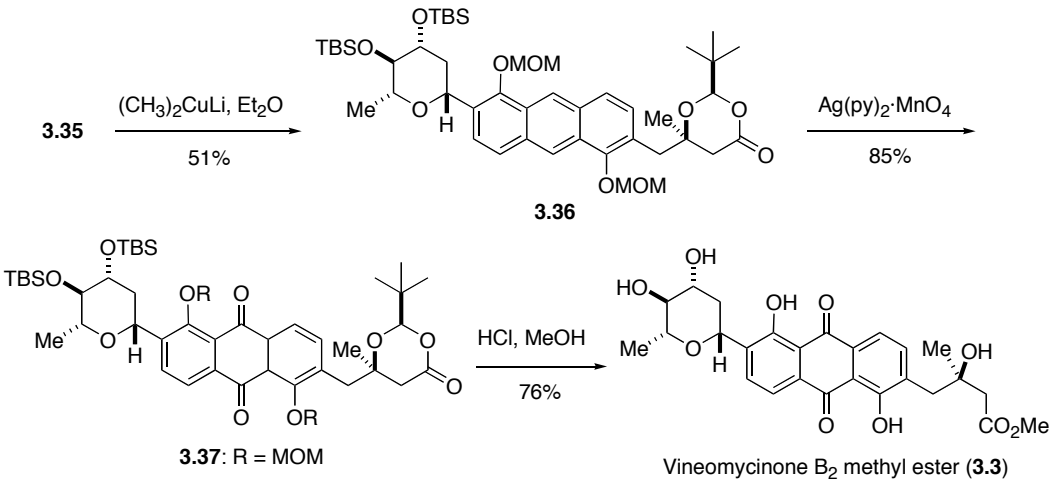
Scheme 3.6



The sterogenic center on the side chain was generated by addition of lithium dimethylcuprate to **3.35** to give **3.36** as a single diastereomer (Scheme 3.7).[149] Oxidation of **3.36** with $Ag(py)_2 \cdot MnO_4$ provided anthraquinone **3.37**.[150] Finally, upon treatment of

3.37 with HCl in anhydrous methanol, all protecting groups were removed, and transesterification occurred to furnish vineomycinone B_2 methyl ester (**3.3**).

Scheme 3.7



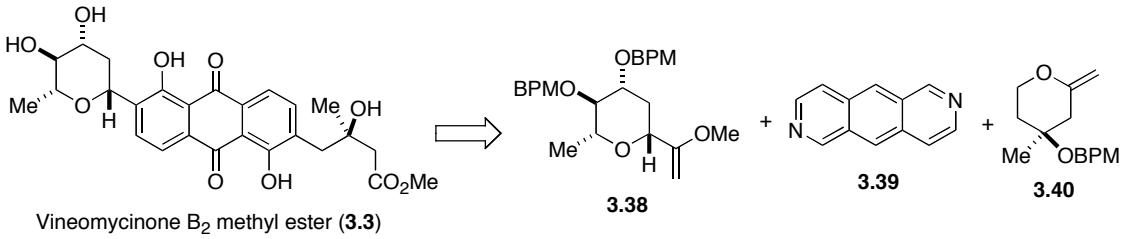
Tius' synthesis features the application of a Nigishi coupling with glucal zinc **3.30** and Stille coupling with allyl bromide **3.34** to introduce an olivose and mevalonate unit on anthrarufin, respectively, which allowed the rapid assembly of vineomycinone B_2 methyl ester. The installation of anomeric proton and tertiary carbon on aliphatic chain was accomplished in high enantioselectivities. In summary, the total synthesis was completed in a total of 22 steps in 0.7% yield from commercially available materials. The longest linear sequence required 16 steps and proceeded in 4% overall yield.

3.4 FALCK'S TOTAL SYNTHESIS OF VINEOMYCINONE B_2 METHYL ESTER

Falck's[151] synthesis of vineomycinone B_2 methyl ester exploited Bradsher cycloadditions.[143e] The vineomycinone skeleton was derived from two consecutive Bradsher cycloadditions of the electron-rich dienophiles **3.38** and **3.40** with isoquinoline **3.39**, in which the glycosyl and hydroxyisovaleryl subunits were set on the anthrarufin

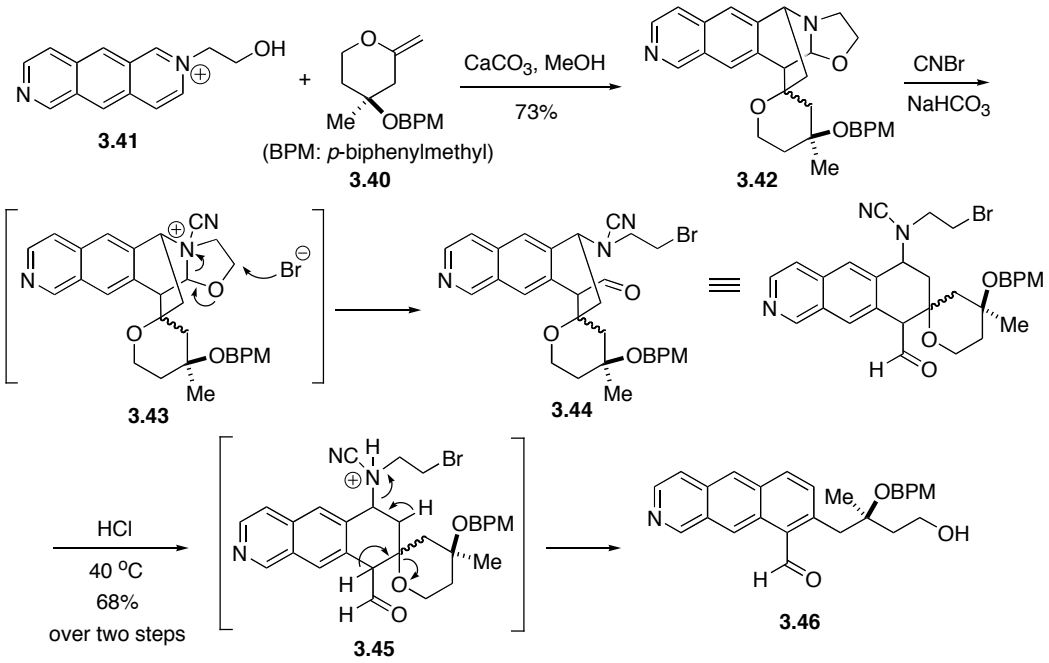
core (Scheme 3.8). Although Falck's synthesis seemed concise and straightforward, the syntheses of fragments **3.38** and **3.40** required seven and eight manipulations, respectively.

Scheme 3.8



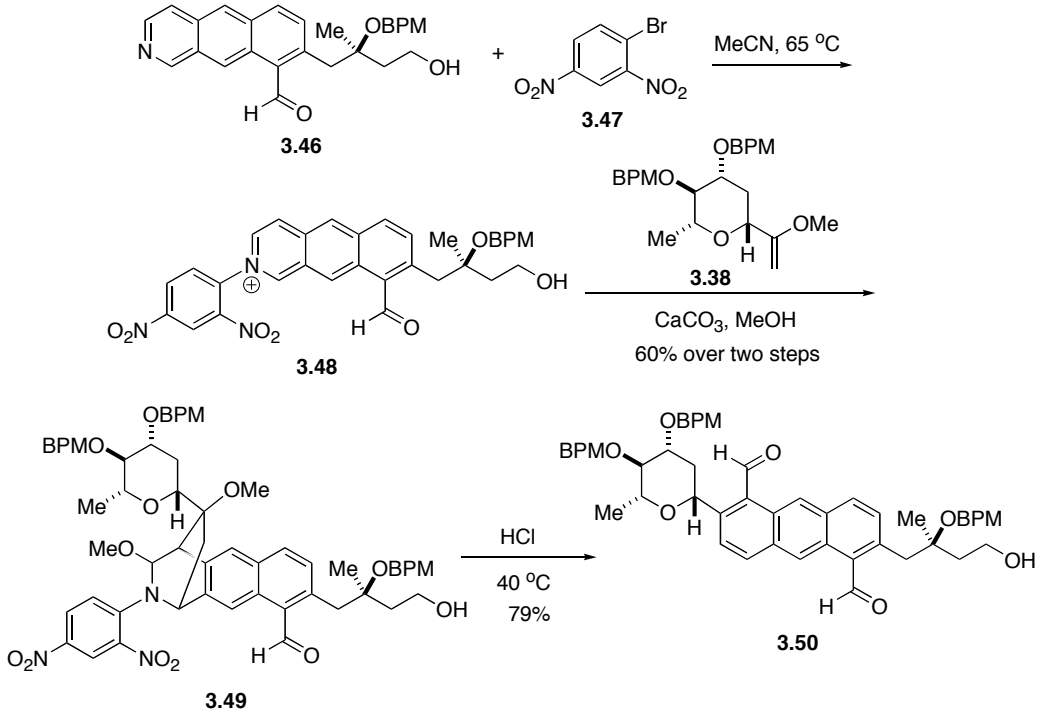
Alkylation of **3.39**[18] with 2-bromoethanol provided isoquinoline salt **3.41**. A Bradsher cyclization between **3.40** and **3.41** in the presence of $CaCO_3$[152] as an acid scavenger, followed by nucleophilic addition of an oxygen atom to the resultant iminium ion provided a mixture of *endo* and *exo* adducts **3.42** (Scheme 3.9).[153] Treatment of **3.42** with methanolic cyanogen bromide generated an azaacetal intermediate **3.43**, which underwent selective von Braun cleavage[154] to give a cyanoamine **3.44**. When **3.44** was heated with acid, elimination occurred to deliver the aromatized product **3.46**.

Scheme 3.9



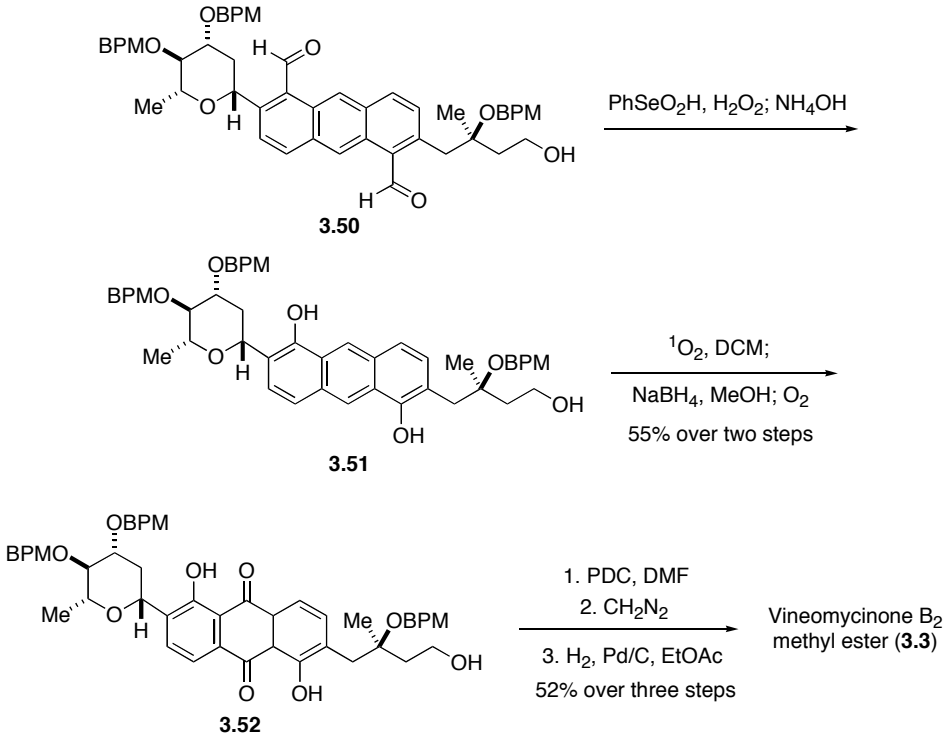
Nucleophilic aromatic substitution of 2,4-dinitrobromobenzene **3.47** with **3.46** gave isoquinoline salt **3.48**,[155] which underwent a second Bradsher cyclization with enol ether **3.38** to furnish cycloadducts **3.49** as a mixture of diastereomers (Scheme 3.10). Acid-catalyzed hydrolysis of the crude cycloadducts thus obtained gave the aromatized product **3.50**, which contained the complete carbon framework of the target molecule.

Scheme 3.10



The residual aldehyde groups were removed under the modified Dakin oxidation conditions to yield anthracinedione **3.51** (Scheme 3.11).[156] Singlet oxygen addition across the central aromatic ring of **3.51**, followed by reductive work-up and air oxidation generated the anthraquinone **3.52**. [157] Oxidation of the primary alcohol in **3.52** with PDC generated an acid, which was transformed to the desired methyl ester upon treatment with diazomethane. Global deprotection of the BMP groups by hydrogenolysis provided vineomycinone B_2 methyl ester (**3.3**).

Scheme 3.11



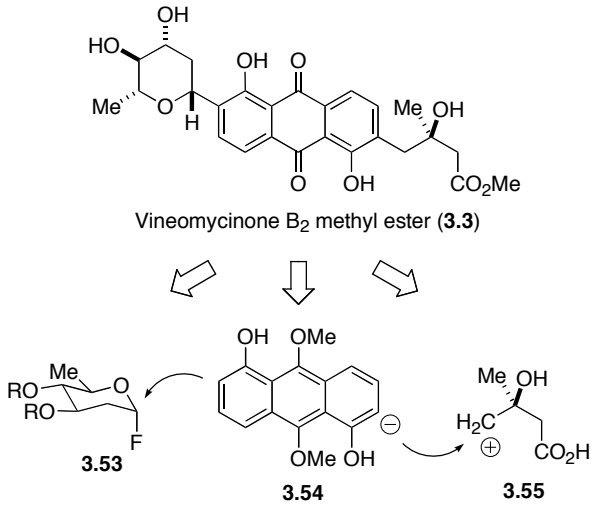
Two Bradsher cycloadditions of an isoquinoline with vinyl enol ethers bearing highly functionalized substituents and subsequent aromatization led to 2,7-disubstituted anthracene **3.50**, in which *C*-aryl glycosyl and hydroxyisovaleryl fragments were regioselectively set on the anthracene core. Anthracene **3.50** was then elaborated to form vineomycinone B_2 methyl ester in five steps. This synthesis required a total of 28 steps and proceeded in 0.09% yield from commercially available materials, and 19 steps in 0.6% yield in the longest linear sequence.

3.5 SUZUKI'S TOTAL SYNTHESIS OF VINEOMYCINONE B_2 METHYL ESTER

Suzuki utilized an O→C glycoside rearrangement[158] as the key step for the total synthesis of vineomycinone B_2 methyl ester.[143f] The retrosynthetic analysis shows the target structure can be divided into three moieties: the sugar **3.53**, anthracene **3.54** and the

aliphatic side chain **3.55** (Scheme 3.12). The key strategy for construction of the aryl *C*-glycoside linkage was the O→C glycoside rearrangement. The alkyl side chain was introduced through directed *ortho* metalation of the anthracene derivative followed by nucleophilic addition with an aliphatic synthon.

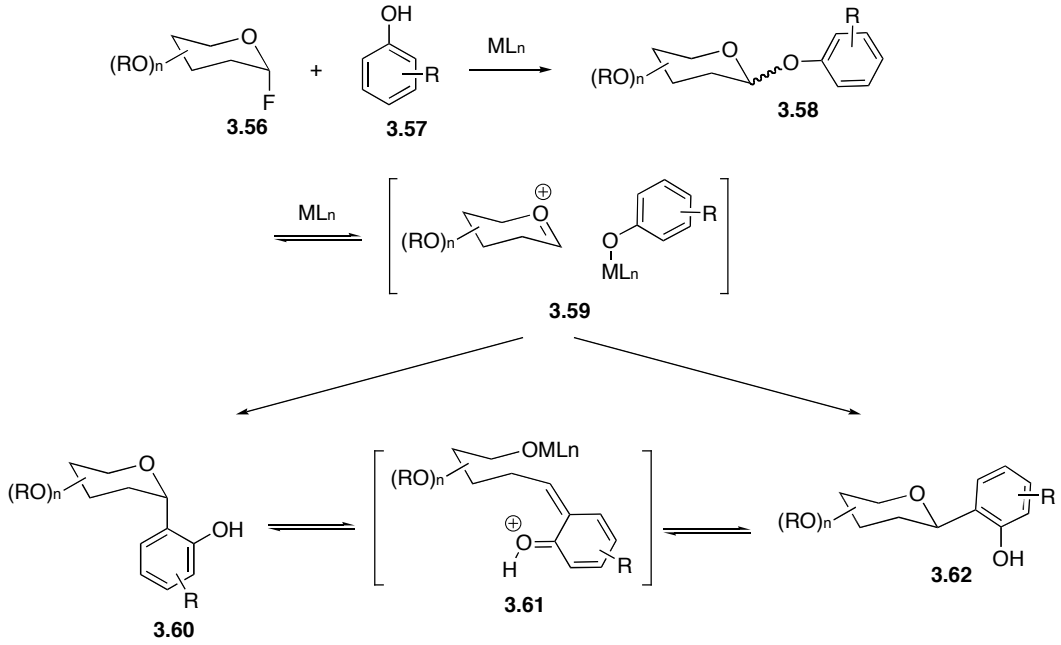
Scheme 3.12



The key feature of the O→C glycoside rearrangement is illustrated in Scheme 3.13.[143,159,160,161] In the presence of an appropriate Lewis acid catalyst, the *O*-glycosidation of phenol **3.57** with glycosyl fluoride **3.56** proceeds at low temperature to give *O*-glycoside **3.58**. By raising the reaction temperature, *O*-glycoside **3.58** is converted *in situ* to *C*-glycosides **3.60** and **3.62**. The O→C glycoside rearrangement occurs *via* ion pair **3.59**, generated from *O*-glycoside **3.58**, which undergoes an irreversible Friedel-Crafts coupling at the *ortho* position to the phenolic hydroxyl group. The high *ortho* selectivity is the remarkable feature of the reaction, whereas some variants provide *para* substituted products.[159] Suzuki rationalizes that α isomer **3.60**, derived from substitution at the anomeric axial position, is the kinetic product. However, Lewis acid-catalyzed

epimerization *via* ring opening-reclosure process provides the thermodynamically favored product **3.62**. The **3.60**/**3.62** ratio is affected by several parameters, such as Lewis acids, ligands, coordination states, stability of **3.60** and **3.62** toward the Lewis acids, and reaction temperatures. The O→C glycoside rearrangement has been applied in the total synthesis of several *C*-aryl glycoside natural products.[162] The O → C-glycoside rearrangement usually requires electron-rich phenols and suitable sugar substrates.

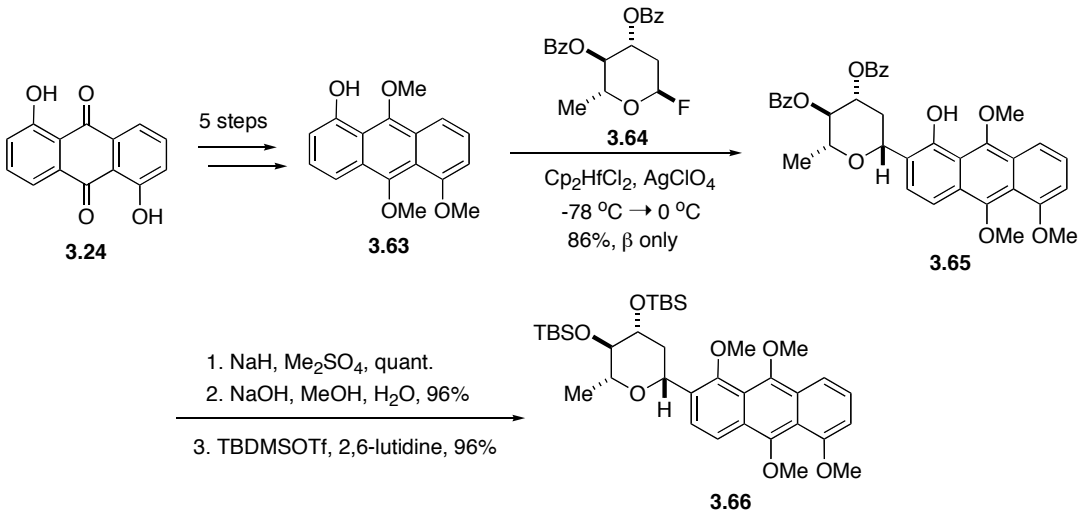
Scheme 3.13



Suzuki's total synthesis of vineomycinone B_2 methyl ester commenced with anthrol **3.63**, which was prepared in five steps from known anthrarufin **3.24**.[143] A solution of sugar **3.64**, which was prepared from commercial triacetyl D-glucal in 9 steps, in CH_2Cl_2 was added to a solution of anthrol **3.63** in the presence of catalytic amount of $Cp_2HfC_{12}{\cdot}AgClO_4$ at -78 ºC. The mixture was then allowed to warm to 0 ºC, whereupon O→C rearrangement occurred to afford solely the β isomeric *C*-glycoside **3.65** in 86%

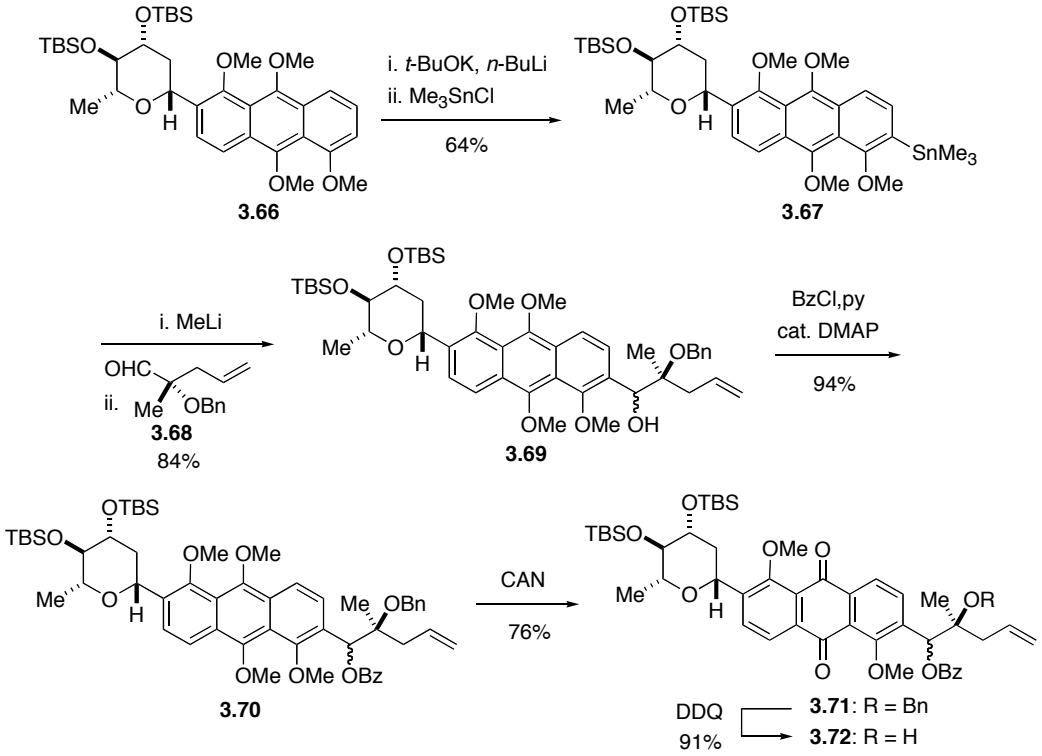
yield; no *O*-glycoside product was observed. Thus, a regio- and stereocontrolled route to the *C*-glycoside sector of the target was established. For further elaboration, the phenolic hydroxyl group of **3.65** was protected as a methyl ether. Removal of the two benzoyl groups under basic conditions followed by silylation employing TBSOTf and 2,6-lutidine gave anthracene **3.66**.

Scheme 3.14



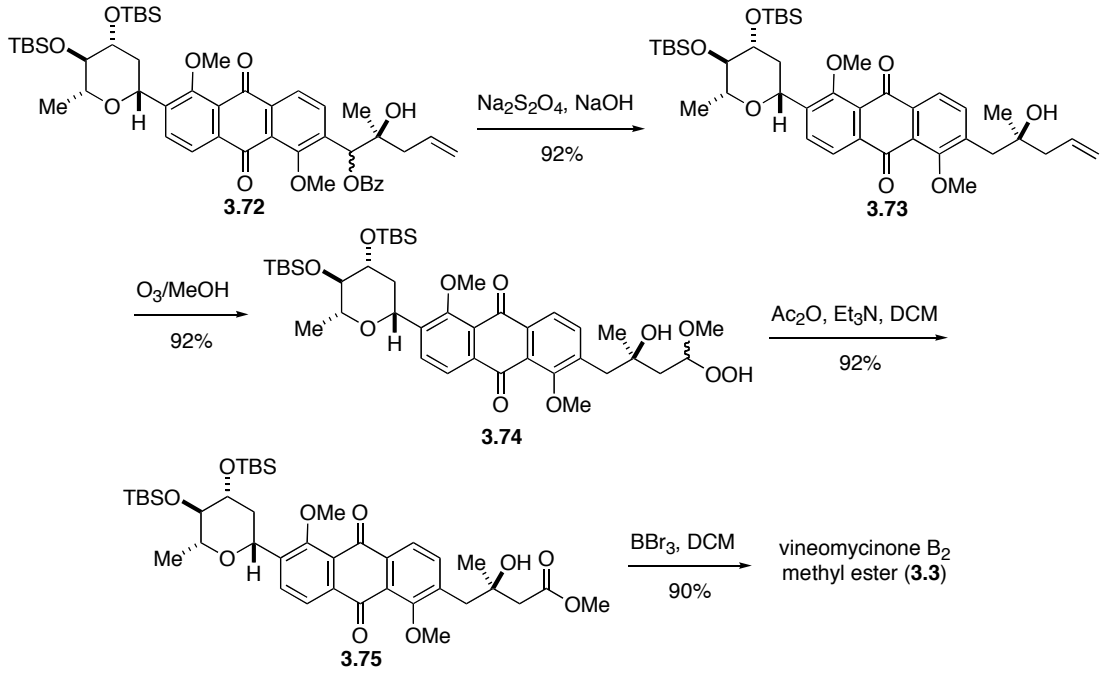
The next task was to install the alkyl side chain. Toward that end, anthracene **3.66** was selectively deprotonated with *t*-BuOK and *n*-BuLi in THF,[163] and the resultant anion was treated with Me_3SnCl to give stannane **3.67**. Lithiation of **3.67** followed by trapping with aldehyde **3.68** furnished anthracene **3.69** as a mixture of diastereomers (2:1). Esterification of **3.69** with BzCl and pyridine in the presence of catalytic DMAP provided benzoate **3.70**. Oxidation of the anthracene core to anthrarufin using CAN and subsequent cleavage of the benzyl group with DDQ gave benzoate **3.72**.

Scheme 3.15



The final stage of the synthesis required selective reduction of the benzylic oxygen, oxidation of the olefin, and removal of the protecting groups. Treatment of benzoate **3.72** with $Na_2S_2O_4$ under slightly basic conditions gave deoxygenated adduct **3.73**, which underwent ozonolysis to afford a diasteromeric mixture of hydroperoxides **3.74**. Treatment of **3.74** with $Ac_2O{\cdot}Et_3N$[164] in CH_2Cl_2 delivered methyl ester **3.75** and subsequent deprotection of methyl and *tert*-butyldimethylsilyl groups with BBr_3 furnished vineomycinone B_2 methyl ester (**3.3**).

Scheme 3.16



This synthesis features the O→C glycoside rearrangement to generate a *C*-aryl glycoside bond at the *ortho* position of anthrolic hydroxyl group, and a selective metalation at the *ortho* position of anthracenic methoxy group followed by reaction with an aldehyde to introduce an aliphatic side chain. These strategies thus led to a convergent total synthesis of vineomycinone B_2 methyl ester. This synthesis was completed in a total of 32 steps in 0.8% yield from commercially available materials. The longest linear sequence required 22 steps and proceeded in 3.3% yield.

3.6 CONCLUSION

Four total syntheses of vineomycinone B_2 methyl ester have been reported.[143] These successful syntheses were attributed to the efficient formation of carbon-carbon bonds at C2 and C6 positions of an anthrarufin, and generation of stereogenic centers. Among of these tasks, the construction of *C*-aryl glycosyl bonds at the *ortho* position of anthrarufinic hydroxyl group is the most challenge one. Several tactics were developed for the generation of *C*-aryl glycosyl bonds such as Diels-Alder cycloadditions, Nigishi cross coupings, Bradsher cycloadditions, and O→C glycoside rearrangements.

Although four total syntheses of vineomycinone B_2 methyl ester have been reported,[143] there remains ample opportunity for the development of new chemistries to access this molecule. The Chapter 4 will detail a convergent total synthesis of vineomycinone B_2 methyl ester. The synthesis features the use of silicon tethers as disposable linkers to control the regiochemistry in two tandem Diels-Alder reactions of substituted benzynes and glycosyl furans. This strategy has provided rapid access to the anthrarufin framework, which contains olivose derivative and aliphatic side chain at C2 and C6 positions, respectively. Manipulations of Diels-Alder adducts easily led to the synthetic vineomycinone B_2 methyl ester.

Chapter 4. Studies toward the Total Synthesis of Vineomycinone B_2 Methyl Ester

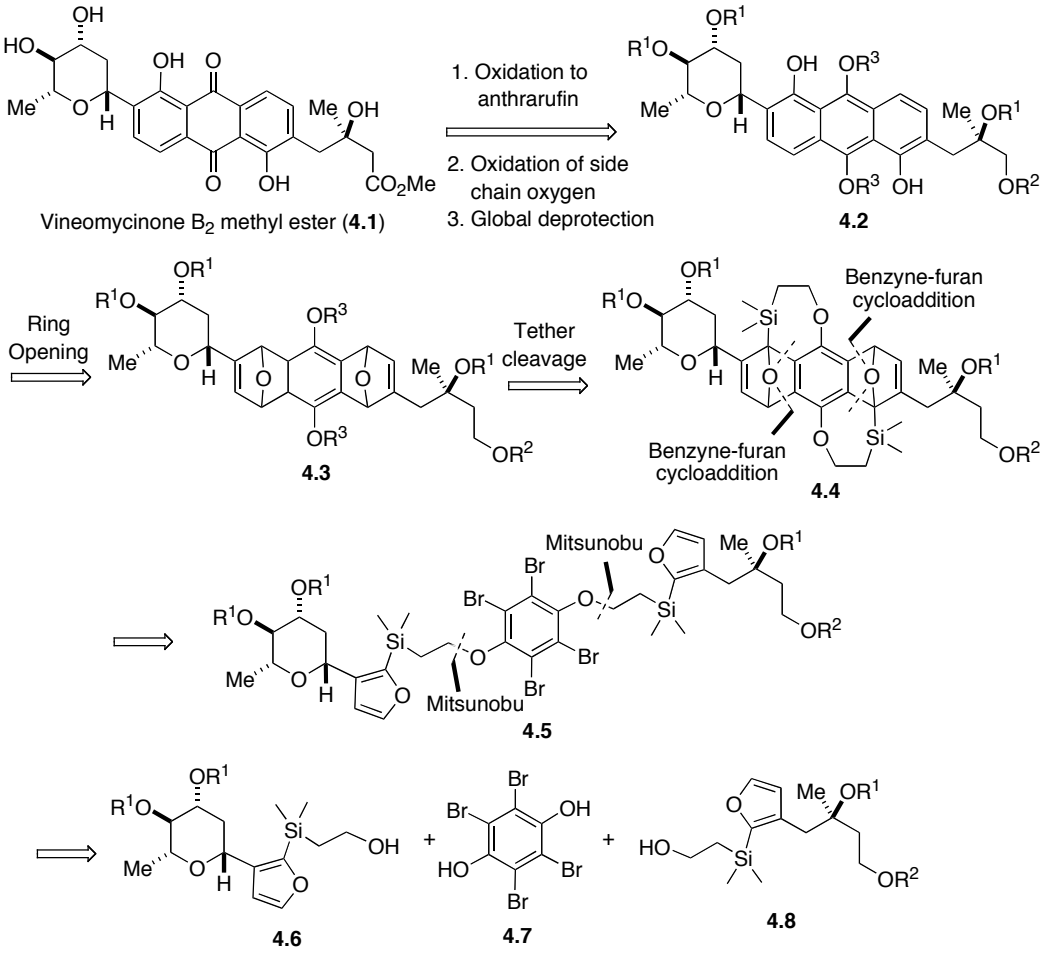
4.1 First Generation Approach toward Vineomycinone B_2 Methyl Ester

Our research group recently developed a general entry to the four major groups of *C*-aryl glycosides (see Chapter 1.10.1).[90a] The strategy features the ring opening of cycloadducts that are derived from the Diels–Alder cycloadditions of symmetric benzynes with glycosyl furans.[90a] Since the two substituents on vineomycinone B_2 methyl ester are unsymmetrically positioned on the anthrarufin nucleus, a major challenge lies in controlling the regioselectivity in the Diels–Alder reactions of substituted benzynes and glycosyl furans. Although unsymmetrical benzynes and furans are known to undergo regioselective Diels–Alder reactions, such reactions typically required particular substituents on substrates to inductively direct the regiochemistry of cycloadditions (see Chapter 1.4.3). Our group then employed disposable silicon tethers to link the substituted benzyne and glycosyl furan moieties (see Chapter 1.10.2).[90d] This strategy provided a general solution to control the regiochemical outcome of the Diels-Alder cycloadditions. After establishing the basic elements of the approach, we turned to the task of applying it to the syntheses of vineomycinone B_2 methyl ester.

On the basis of that advance, a novel and highly convergent approach for the preparation of vineomycinone B_2 methyl ester (**4.1**) was designed (Scheme 4.1). It is expected that the tandem intramolecular benzyne–furan cycloadditions would assemble the anthrarufin framework in a *single* operation. We envisioned that vineomycinone B_2 methyl ester (**4.1**) could arise from anthracendiol **4.2** *via* oxidation of anthracene ring to anthrarufin, oxidation of the alkyl side chain and global removal of the oxygen protecting groups. The anthracendiol **4.2** could be prepared from regioselective ring opening of **4.3**

that in turn could be prepared from bisoxabenzonorbornadiene **4.4** through silicon tether cleavage. Bisoxabenzonorbornadiene **4.4** would be derived from cycloaddition of bisbenzyne precursor **4.5**. The Diels-Alder precursor **4.5** would arise from the iterative Mitsunobu coupling of tetrabromohydroquinone (**4.7)** with the silicon-substituted furans **4.6** and **4.8**, both of which would be prepared from readily available starting materials.

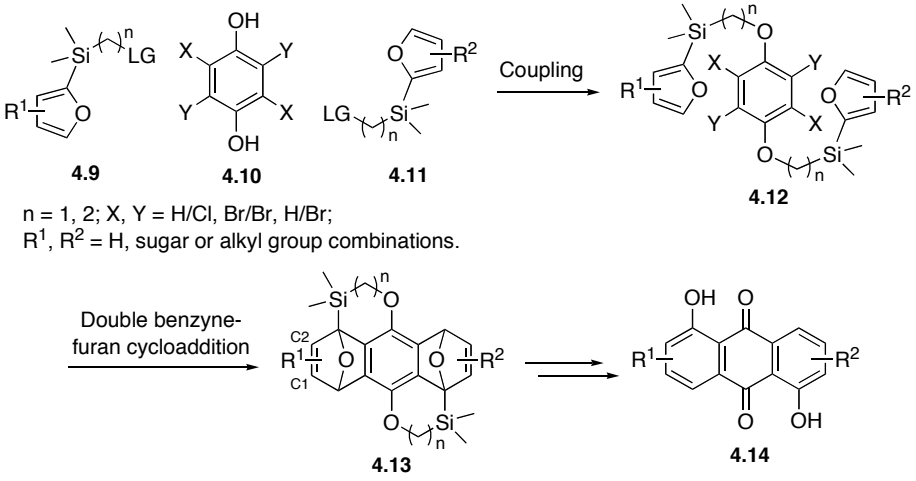
Scheme 4.1



Prior to achieving the synthesis of vineomycinone B_2 methyl ester, several important issues needed to be considered. The first was to determine a suitable benzyne precursor **4.12** for a double benzyne-furan cycloaddition (Scheme 4.2). We envisoned

that **4.12** was derived from the coupling of furans **4.9** and **4.10** with hydroquinone **4.11**. X and Y on **4.12** should be easily eliminated to give a benzyne intermediate under mild conditions. Chloroaromatic derivatives were used as benzyne precursors in our preliminary *C*-aryl glycoside synthesis.[90d] Hart has demonstrated that tetrabromobenzenes serve as bisbenzyne precursors in Diels–Alder reaction.[165] There are also several examples of cycloadditions proceeding with benzynes generated from bromobenzenes.[166] The combination of X/Y tentatively could be H/Cl, Br/Br or H/Br. Since our group has used the silicon tethers bearing one or two carbon atoms to link the reacting benzynes and furans for the synthesis of *C*-aryl glycosides (see Chapter 1.10.2), we need to ascertain that the number of carbon atoms, n, on benzyne precursor **4.12** would be optimal in the tandem cycloaddition process.

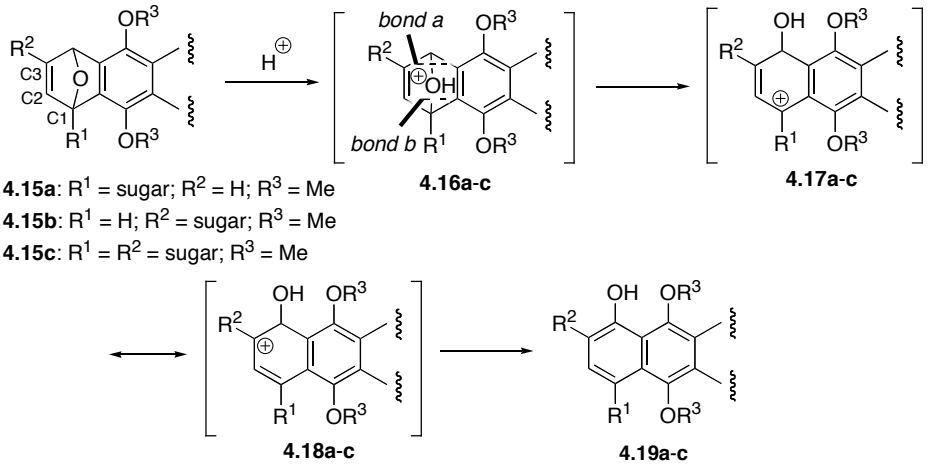
Scheme 4.2



To control the regioselectivity of the ring opening process is the most challenge for the conversion of bisoxabenzonorbornadiene **4.13** to anthrarufin **4.14**. Work from our laboratories has shown that acid-catalyzed regioselective rearrangements of bicyclic compounds **4.15a**-**c**, which contain substituents at the C3 and/or bridgehead C1 position,

furnish *ortho* or *para* naphthols **4.19a-c** (Scheme 4.3, see Chapter 1.10).[90a-d] The regiochemical outcome of ring opening reaction is essentially directed by the R^1 and R^2 groups on oxabenzonorbornadiene **4.15**. The acid-catalyzed rearrangement provided a tertiary cation intermediate **4.17** and/or **4.18** *via* cleavage of *bond b*, and subsequent aromatization delivered product **4.19**. However, the cleavage of *bond a* would yield a secondary cation. Thus, the cleavage of *bond b* is preferentially, which results in the regioselective ring opening reaction.

Scheme 4.3

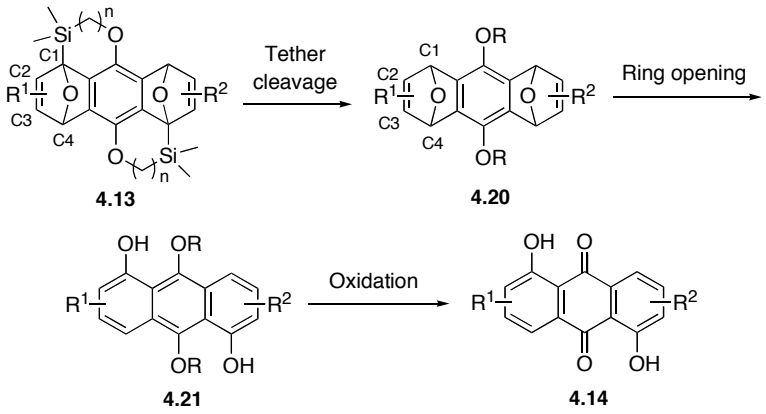


4.15a: R^1 = sugar; R^2 = H; R^3 = Me
4.15b: R^1 = H; R^2 = sugar; R^3 = Me
4.15c: R^1 = R^2 = sugar; R^3 = Me

4.16a-c **4.17a-c** **4.18a-c** **4.19a-c**

Based on these advances, we anticipated that the carbon-silicon bond in **4.13** should be cleaved first, and substituents R^1 and R^2 on oxabenzonorbornadienes would direct the ring opening process to give **4.21** (Scheme 4.4). Subsequent oxidation would deliver anthrarufin **4.14**. For these transformations, both one-carbon and two-carbon tether substrates (n = 1, 2) require different tactics for the removal of silicon tethers, which have been discussed in Chapter 1.10.2.[90d]

Scheme 4.4



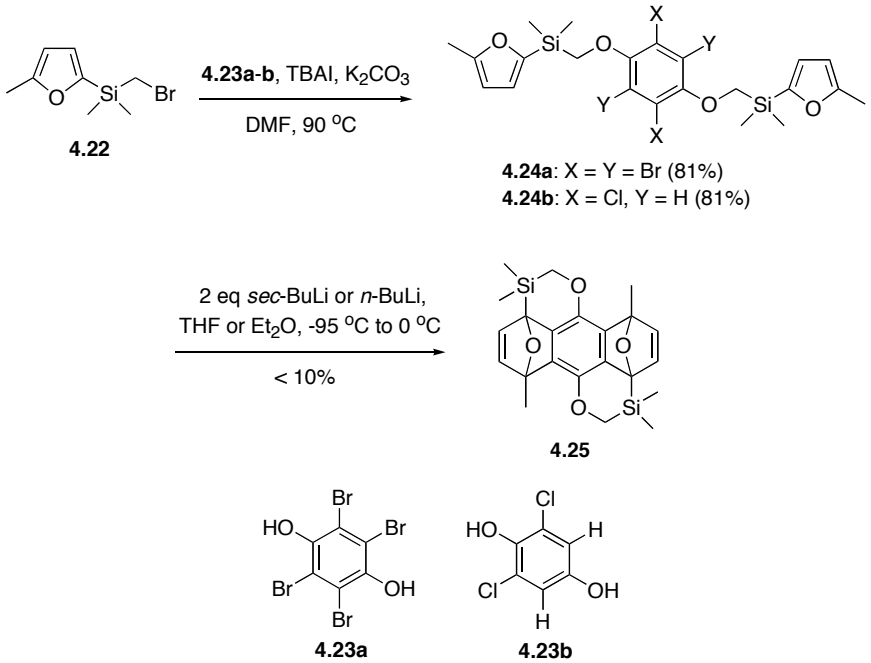
Due to several factors that may affect the efficiency of double benzyne–furan cycloadditions and the conversion of bisoxabenzonorbornadienes to anthrarufins, we decided to explore model studies before moving onto the real system. Preliminary research in our group was conducted by Dr. Steven M. Sparks, a former Martin Group postdoctoral associate. Dr. Sparks established conditions for the regioselective construction of bisoxabenzonorbornadienes *via* double intramolecular silicon tethered benzyne-furan cycloadditions.[167] He has synthesized several bisoxabenzonorbornadienes, including **4.33**, **4.42**, **4.44** and **4.76**. Most of work in our first generation approach was done by Sparks, except exploration of chemistry in Scheme 4.6, optimization of yields for compound **4.39**, and characterization of compounds **4.22**, **4.40** and **4.37** were done by me.

4.1.1 Model benzyne–furan cycloadditions

Model studies were initially conducted by Sparks to evaluate both tetrabromoarene **4.24a** and dicholoroarene **4.24b** as bisaryne precursors bearing a one-carbon tether (α-dimethylsilylmethylene tether). 2,3,5,6-Tetrabromohydroquinone

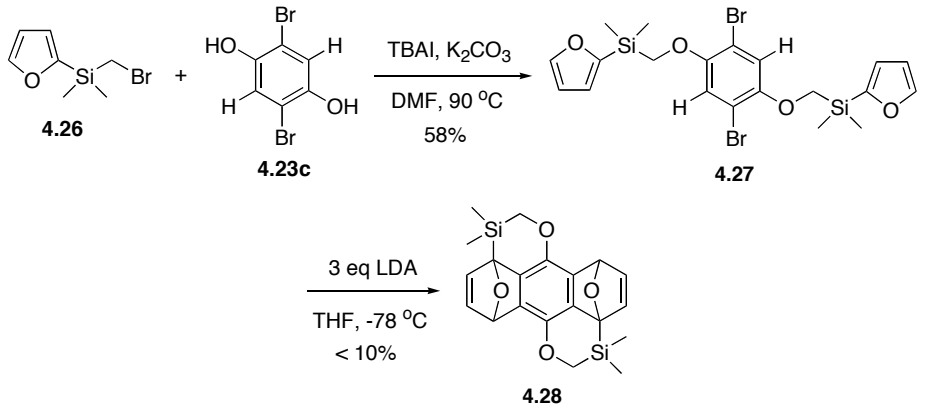
(**4.23a**)[168] and 2,6-dicholorohydroquinone (**4.23b**)[169] were coupled with the furan **4.22**[170] using K_2CO_3 and TBAI in DMF at 90 °C to afford Diels–Alder precursors **4.24a** and **4.24b**, respectively (Scheme 4.5). Tetrabromoarene **4.24a** was first evaluated in the cycloaddition. Treatment of **4.24a** with *n*-BuLi in Et_2O produced a complex mixture of unidentified materials, and less than 10% yield of the desired biscycloadduct **4.25** was isolated. This result led to a screening of reaction conditions in an attempt to obtain higher yields of **4.25**. However, no increase in yield was observed upon changing the solvent (THF, toluene), temperature (0 °C to room temperature), or including additives (TMEDA). Dichloroarene **4.24b** was then examined for the double benzyne-furan cycloaddition. Unfortunately, treatment of **4.24b** with *sec*-BuLi or *n*-BuLi at low temperatures provided several unidentified products, and no cycloadduct **4.25** was obtained.

Scheme 4.5



We turned the attention to explore the feasibility of a dibromoarene **4.27** as benzyne precursor. In earlier attempts, treatment of *p*-dibromohydroquinone **4.23c**[171] with alkyl bromide **4.26**[172] in DMF at 90 ºC resulted in the decomposition of hydroquinone **4.23c**, presumably due to the instability of electron-rich hydroquinone **4.23c** toward the base and air (Scheme 4.6). When the reaction was performed in degassed DMF under argon, disubstituted aryl ether **4.27** was obtained in good yield. Unfortunately, treatment of **4.27** with LDA in THF at –78 ºC provided cycloadduct **4.28** in less than 10% yield together with several unidentified materials.

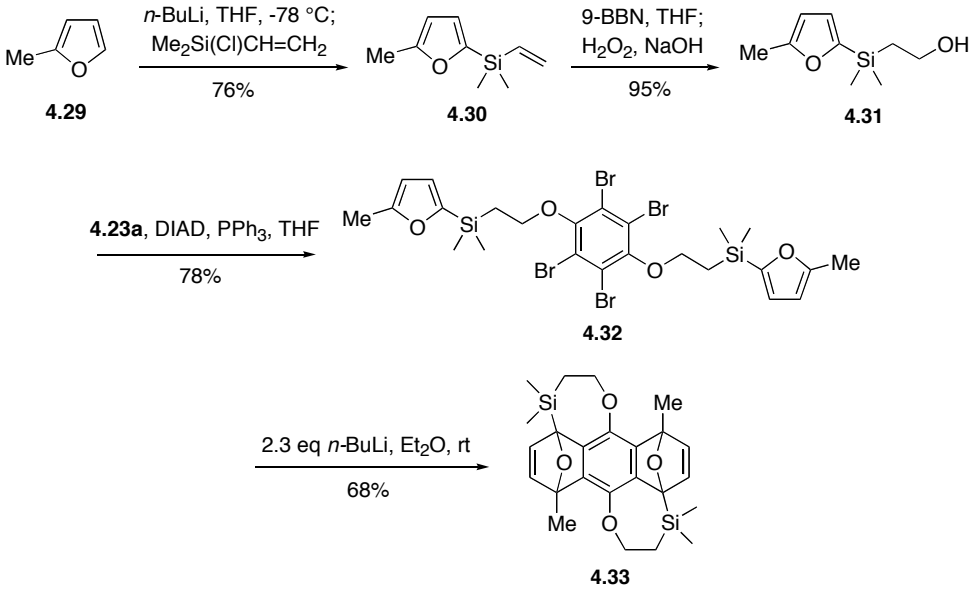
Scheme 4.6



The disappointing yields in these cycloaddition could be attributed to the highly strained system of the biscycloadducts **4.25** and **4.28.** At this point, we decided to explore the cycloaddition with benzyne precursor **4.32** in which silicon tethers contain two methylene groups. Toward that end, deprotonation of **4.29** with *n*-BuLi followed by trapping of resultant anion with commercially available chlorodimethylvinylsilane provided a vinylsilane **4.30**, which was hydroborated employing 9-BBN and oxidized (NaOH, H_2O_2) to afford the alcohol **4.31** in 95% yield over the two steps (Scheme 4.7).[173] Mitsunobu coupling of **4.31** and *p*-tetrabromohydroquinone **4.23a** using

diisopropyldiazodicarboxylate and triphenylphosphine afforded **4.32** in 78% yield. Cycloaddition occurred upon treatment of **4.32** with *n*-BuLi in Et_2O to furnish the biscycloadduct **4.33** in 68% yield. This is the first successful example of a double intramolecular benzyne-furan cycloaddition to form a bisoxabenzonorbornene in a single operation.

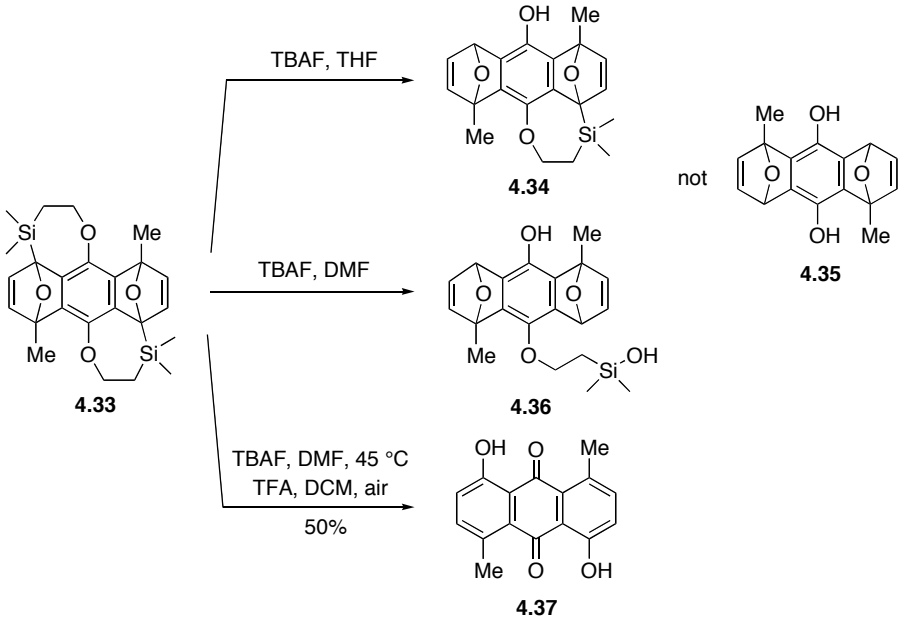
Scheme 4.7



We next explored the complete removal of the β-dimethylsilylethyl tethers in cycloadduct **4.33**. Treatment of **4.33** in THF with excess TBAF provided a mixture of diasteriomeric phenols **4.34**, arising from removal of one β-dimethylsilylethyl tether in **4.33** (Scheme 4.8). Changing the solvent to DMF led to the isolation of phenol **4.36**, resulting from the cleavage of both bridgehead carbon-silicon bonds with one of the remaining β-dimethylsilylethyl residues further fragmenting to unmask the phenol. Since the desired product **4.35** was not isolated from these reactions, we decided to treat the crude reaction mixtures with protic acid to open the oxabenzonorbornene rings.

Treatment of cycloadduct **4.33** with TBAF in DMF at 45 °C followed by subjection of the crude reaction mixture to acid-catalyzed ring opening (TFA, CH_2Cl_2) afforded the desired anthrarufin **4.37** in 50% overall yield. The formation of **4.37** indicated that the ring opening process was regioselectively directed by the methyl group and the resultant ring-opened products underwent an aerobic oxidation. This result successfully demonstrated the conversion of bisoxabenzonorbornadiene to anthrarufin *via* protiodesilylation followed by regioselective ring opening and oxidation.

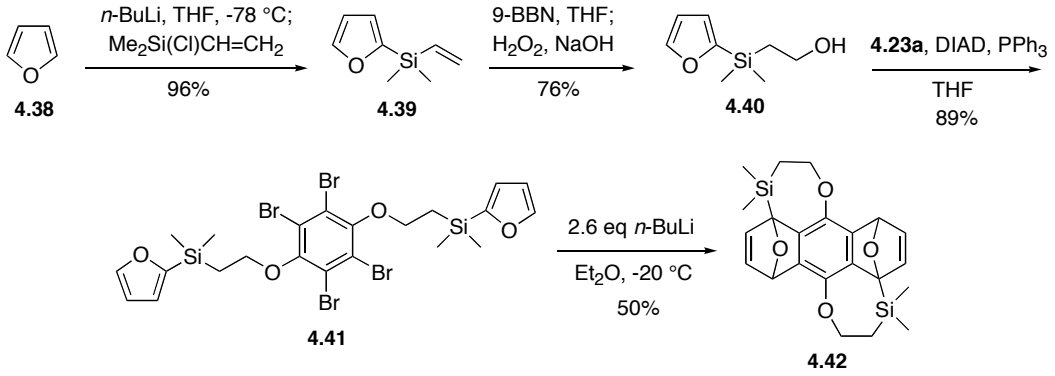
Scheme 4.8



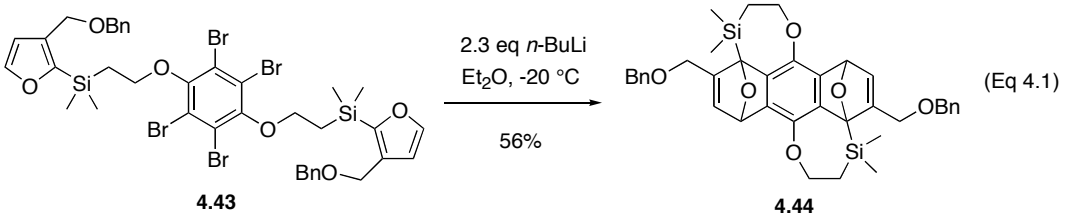
Variation of substitution on the furan was then investigated. The synthesis of biscycloadduct **4.42** commenced with furan **4.38** (Scheme 4.9). Metallation of furan **4.38** with *n*-BuLi in THF followed by trapping with dimethylchlorovinylsilane provided **4.39** in 96% yield. Sequential hydroboration of **4.39**,[173] followed by Mitsunobu coupling provided Diels–Alder precursor **4.41** in 68% yield over two steps. Hydroquinone **4.41** in toluene (0.02 M) was treated with two equivalents of *n*-BuLi at room temperature to

afford 27% yield of biscycloadduct **4.42** as a mixture of diastereomers and 14% yield of monocycloadduct. Changing the reaction solvent to Et_2O (0.02 M) increased the yield of **4.42** to 32% together with 23% of monocycloadduct. Gratifyingly, treatment of hydroquinone **4.41** with excess *n*-BuLi (2.6 eq) in Et_2O (0.02 M) at -20 °C until all monocycloadduct was consumed as determined by TLC, gave **4.42** in 50% yield.

Scheme 4.9



After the demonstrating that both C5 substituted and unsubstituted furans **4.32** and **4.41** are tolerated in the key biscycloaddition step, the feasibility of using furan **4.43** with substituent at the C3 position was examined (Eq 4.1). Treatment of Diels-Alder precursor **4.43**[174] with *n*-BuLi provided cycloadduct **4.44** in 56% yield.



(Eq 4.1)

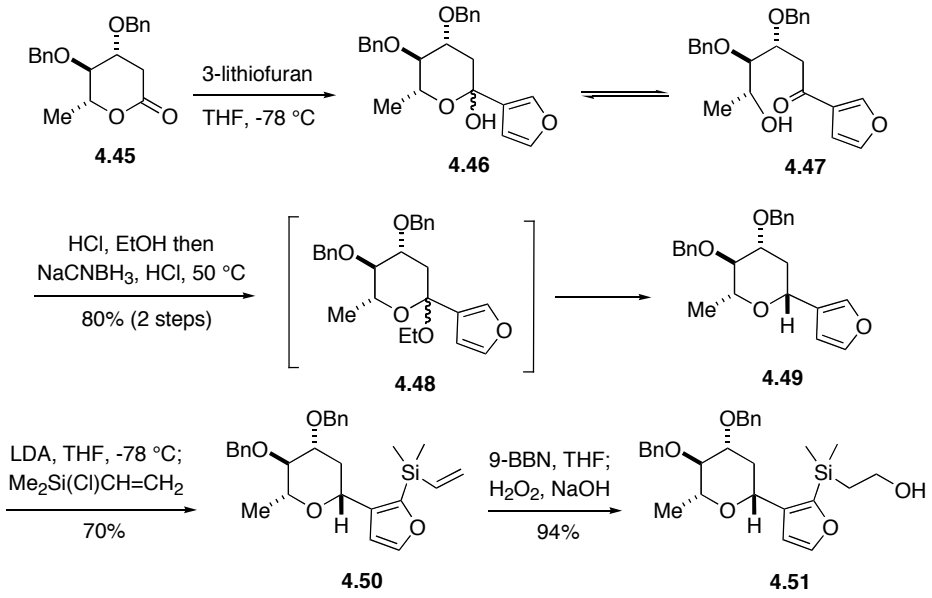
In summary, the efficiency of model double intramolecular benzyne–furan cycloadditions were established with two-carbon (**4.32**, **4.41**, and **4.43**) and one-carbon tethered substrates (**4.24a**-**b** and **4.27**), although the yields were much lower for the latter.

Conversion of the bisoxabenzonorbornadiene **4.33** to anthrarufin **4.37** was successfully achieved. Based upon these advances, we turned to the more challenging task of the total synthesis of vineomycinone B_2 methyl ester (**4.1**) according to the plan outlined in Scheme 4.1, utilizing a two-carbon tether linkage to control the regiochemistry of the Diels-Alder reaction.

4.1.2 Studies toward the Total Synthesis of Vineomycinone B_2 Methyl Ester

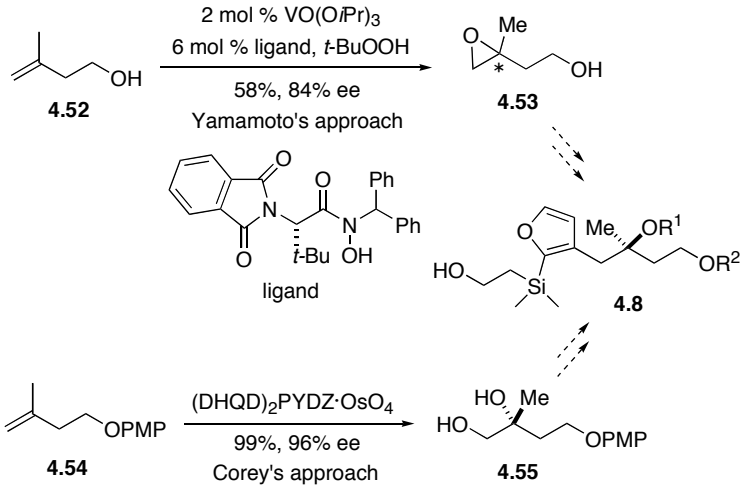
The first phase of our work toward the syntheses of vineomycinone was initiated by the preparation of substituted furan **4.6** and **4.8**. Since the late stages of the synthesis would involve a global removal of all hydroxyl protecting groups, we envisioned that benzyl ethers would be well suited to the task. The glycosyl furan **4.51** thus appeared as our initial objective. The synthesis of **4.51** commenced with the addition of 3-lithiofuran to the known lactone **4.45**[90c] to afford a mixture of lactols **4.46**, which were in equilibrium with the open keto-alcohol **4.47** (Scheme 4.10). This mixture was then treated with ethanolic-HCl to furnish ethyl acetal intermediates **4.48** that were stereoselectively reduced upon treatment with $NaCNBH_3$ in ethanolic-HCl at 50 °C to yield glycosylfuran **4.49** in 80% overall yield.[175] Regioselective lithiation[90d,176] of **4.49** directed by the glycosyl oxygen, and trapping of the resultant anion with chlorodimethylvinylsilane generated the vinyl silane **4.50**, which was subjected to hydroboration/oxidation[173] to provide furan **4.51** in 66% yield over two steps.

Scheme 4.10



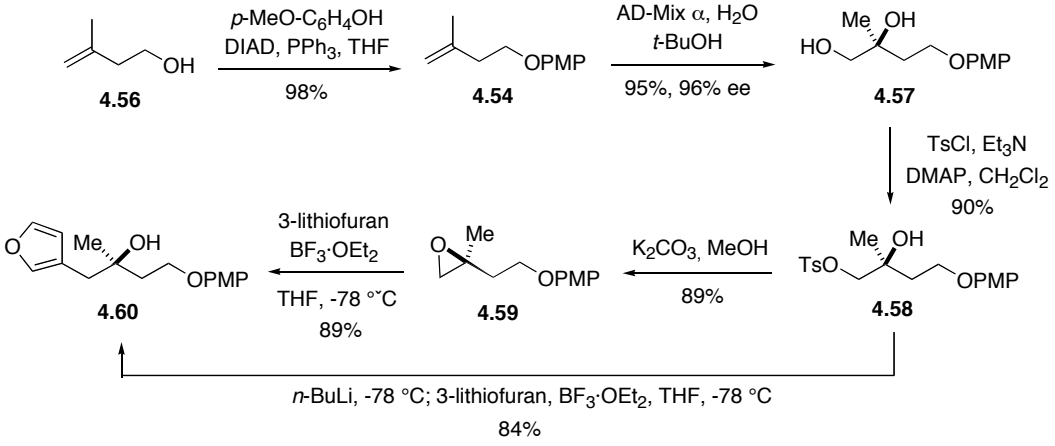
Turning to the synthesis of furan **4.8**, efforts were initially focused on enantioselectively installing the tertiary chiral center. There are two potential approaches to construct the desired asymmetric framework (Scheme 4.11). A highly enantioselective epoxidation of homoallylic alcohols using a chiral vanadium catalyst was reported by Yamamoto.[177,178] Utilizing 3-methyl-3-butenol **4.52** as a substrate, Yamamoto was able to obtain epoxide **4.53** in 58% yield and 84% enantiomeric excess. Corey expanded the scope of Sharpless asymmetric dihydroxylation to homoallylic alcohol derivatives.[179] Asymmetric dihydroxylation of 1-(4-methoxyphenoxy)-3-methyl-3-butene **4.54** using $(DHQD)_2PYDZ{\cdot}OsO_4$ as catalyst provided diol **4.55** in 99% yield and 96% enantiomeric excess. After comparing these two approaches, we decided to apply Corey's method to prepare tertiary alcohol **4.55** since it provided better enantioselectivities.

Scheme 4.11



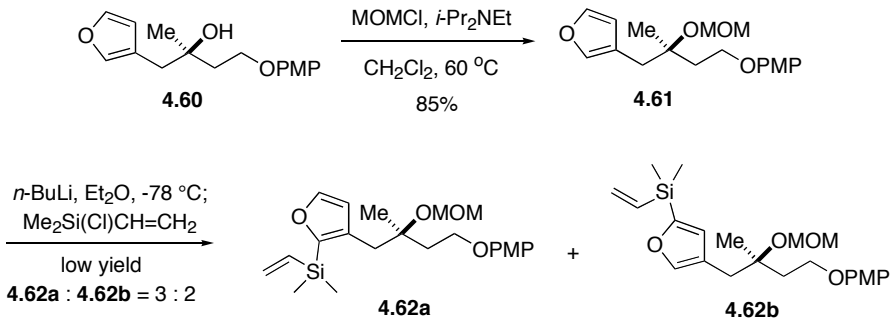
3-Methyl-3-butenol **4.56** was first protected as its PMP ether **4.54**, which was subjected to Sharpless asymmetric dihydroxylation conditions using AD-Mix α to afford diol **4.57** in 93% yield over two steps (96% ee) (Scheme 4.12).[179] Treatment of diol **4.57** with tosyl chloride and triethylamine in the presence of a catalytic amount of DMAP afforded primary tosylate **4.58**, which was converted to the epoxide **4.59** in 81% yield over two steps. Opening of epoxide **4.59** with 3-lithiofuran in the presence of $BF_3 \cdot OEt_2$ gave tertiary alcohol **4.60** in 89% yield. Alternatively, the primary tosylate **4.58** was cyclized by deprotonation with *n*-BuLi to give an epoxide intermediate that underwent facile opening *in situ* with 3-lithiofuran in the presence of $BF_3 \cdot OEt_2$ to provide the tertiary alcohol **4.60** in 84% yield.

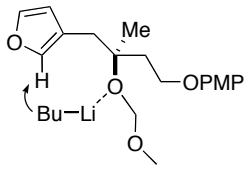
Scheme 4.12



With a reliable method for the preparation of furan **4.60** in hand, examination of the selective attachment of a silyl tether to the 2-position of furan was initiated. The tertiary alcohol **4.60** was protected as a MOM ether **4.61**[180] since MOM ethers show the superior ability to direct metallation reactions (Scheme 4.13).[181] However, metallation of furan **4.61** with *n*-BuLi in Et_2O at –78 °C followed by treatment with chlorosilane provided a mixture 3:2 of furans **4.62a** and **4.62b** in low yield. The low regioselectivity could be attributed to transition state **4.63**, which contains an unfavorable 8-membered ring conformation. Thus, directed deprotonation was not promising, and the reaction provided poor ratio of products.

Scheme 4.13

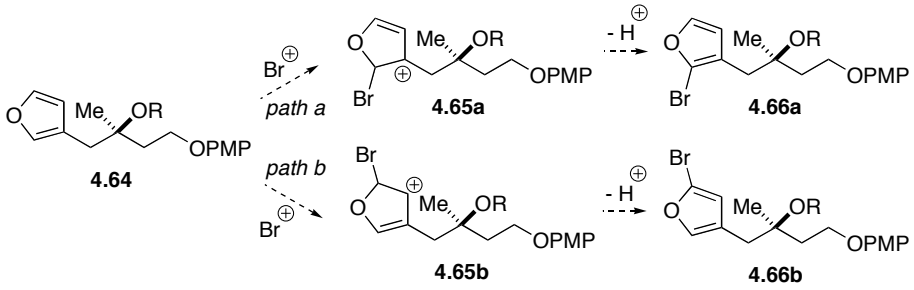




4.63

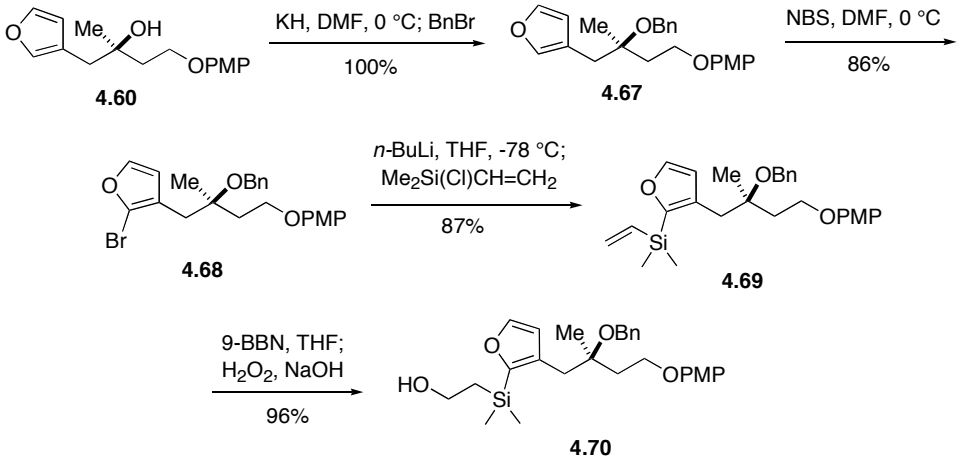
To improve the regioselectivity, the focus was transferred to the electrophilic bromination of furan **4.64**. As shown in Scheme 4.14, we expected *path a* would dominate the bromination of **4.64** since it would provide a more stable tertiary cation intermediate **4.65a**. After deprotonation, it would afford aromatized product **4.66a**. Metal-halide exchange of **4.66a** followed by silylation would yield a 2-silylfuran.

Scheme 4.14



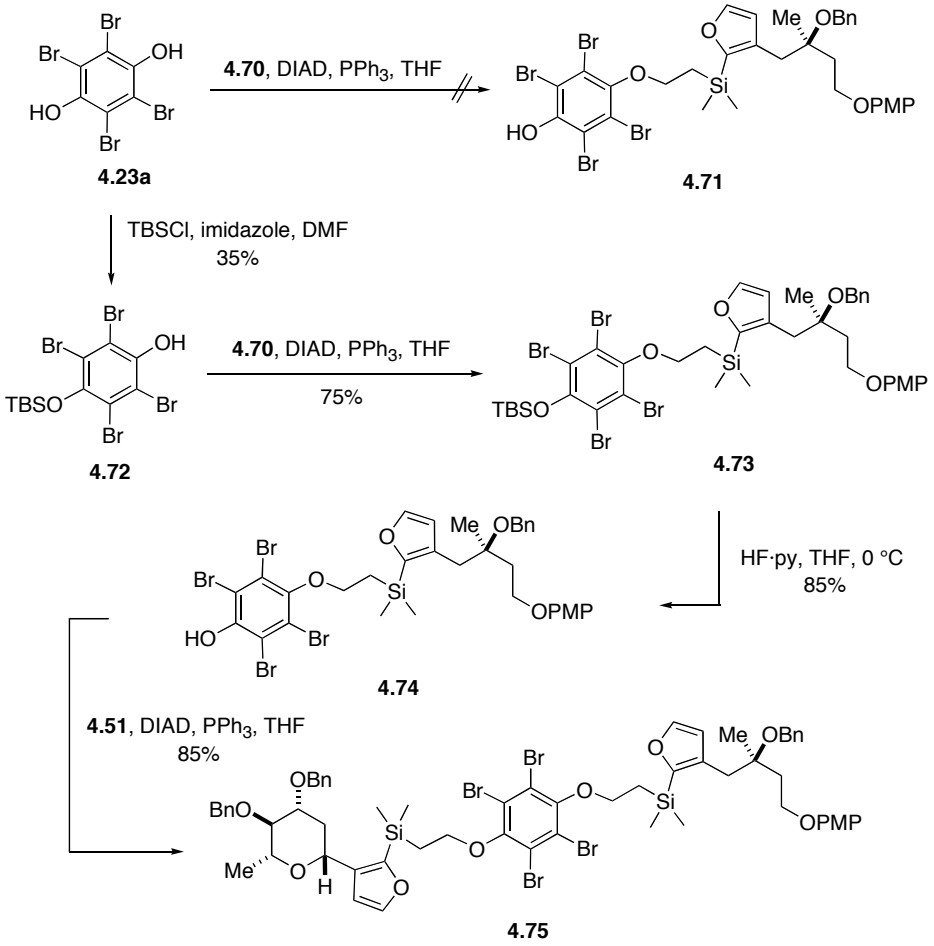
Since protecting the tertiary alcohol **4.60** as a MOM ether **4.61** would not be compatible with our eventual goal to effect a single global deprotection as the final step of the synthesis, **4.60** was converted into **4.67** by *O*-benzylation (Scheme 4.15). Fortunately, highly regioselective bromination of **4.67** was obtained by reaction with NBS to furnish furyl bromide **4.68** in 86% yield over two steps.[182] The bromide **4.68** was subjected to metal-halogen exchange upon treatment with *n*-BuLi. The resultant anion was then trapped with chlorodimethylvinylsilane to afford the vinylsilane **4.69** as the exclusive regioisomer in 87% yield. Subsequent hydroboration and oxidation of the vinyl moiety provided the desired furan **4.70**.[173]

Scheme 4.15

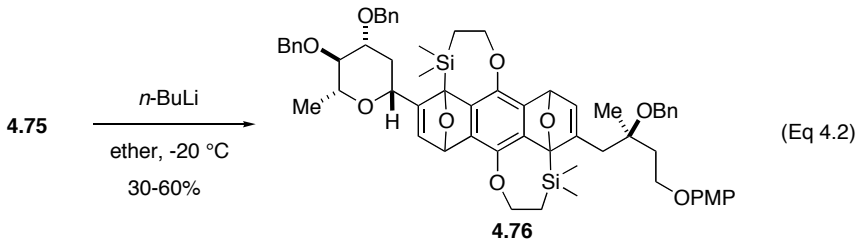


Having prepared the two substituted furans **4.51** and **4.70**, efforts were next focused on the assembly of the Diels–Alder precursor. Treatment of alcohol **4.56** with four equivalents of tetrabromohydroquinone, triphenylphosphine and diisopropylazodicarboxylate in THF provided a complex mixture of unidentified products and recovered **4.70** (Scheme 4.16). To circumvent this problem, monoprotection of hydroquinone **4.23a** was undertaken. Silylation of tetrabromohydroquinone **4.23a** with TBSCl and imidazole in DMF provided phenol **4.72**. In the event, alcohol **4.70** and the phenol **4.72** underwent Mitsunobu coupling employing DIAD and PPh_3 to furnish aryl ether **4.73** in 75% yield. Deprotection of the silyl group utilizing HF·pyridine in THF released the phenol **4.74**, which was then coupled with furan **4.51** via a second Mitsunobu reaction to deliver Diels-Alder substrate **4.75** in 72% yield over two steps.

Scheme 4.16

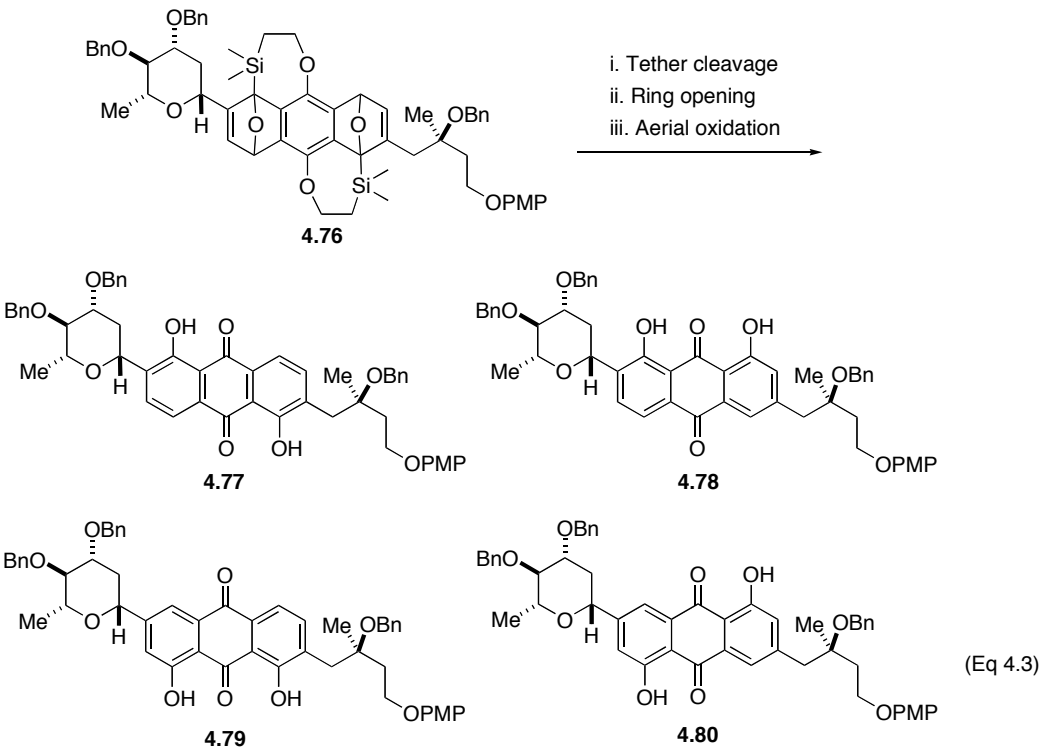


With the Diels–Alder precursor **4.75** in hand, the pivotal double benzyne-furan cycloaddition was examined. Dropwise addition of 2.6 equivalents of a diluted solution of *n*-BuLi (0.23 M) to a solution of tetrabromide **4.75** in Et_2O at –20 °C afforded of a mixture of diastereomeric biscycloaddition product **4.76** in variable yields (30-60%) (Eq 4.2).



(Eq 4.2)

Efforts were directed toward the ring opening and oxidation of the bisoxabenzonorbornene core. Treatment of cycloadduct **4.76** with TBAF in DMF at 60 °C followed by TFA in CH_2Cl_2 led to a mixture of regioisomeric anthraquinones in addition to other unidentified compounds (Eq 4.3).[90d] Unfortunately, desired anthrarufin **4.77** could not be isolated. The ^1H NMR spectrum of the mixture showed the major signals between 8.2-7.9 ppm in the aromatic region consisted of doublets with 1.5 Hz coupling constants. These small coupling constants indicated that phenolic hydroxyl groups were oriented *meta* to substituents on the anthraquinone ring. In addition, the two major signals for the phenolic protons were observed at 12.5 and 12.6 ppm, whereas the two phenolic protons of vineomycinone B_2 methyl ester appear at 13.1 and 13.2 ppm.[143d] Complete removal of the silicon tethers from **4.76** with various fluoride sources (TBAF, TBAT, CsF, HF·py) in different solvents (DMF, THF, dichloromethane, DMSO) at several temperatures (rt, 45 ºC, 60 ºC, 80 ºC) provided a mixture of materials, which were treated with various Lewis acids (TFA, TMSOTf, $BF_3{\cdot}Et_2O$) in several solvents (THF, dichloromethane, toluene) to induce the removal of the tethers and open the bisoxabenzonorbornadienes. Unfortunately, these reactions led to mixtures of unidentified baseline materials. Although Sparks also explored other model systems, these attempts met problems in cylcoadditions, ring openings and/or tether cleavages.[174] Due to the problems encountered in the attempted tether cleavage and ring opening reactions, we decided to modify the sequence of the first generation approach and hoped that the second generation approach might provide the desired anthrarufin **4.77**.



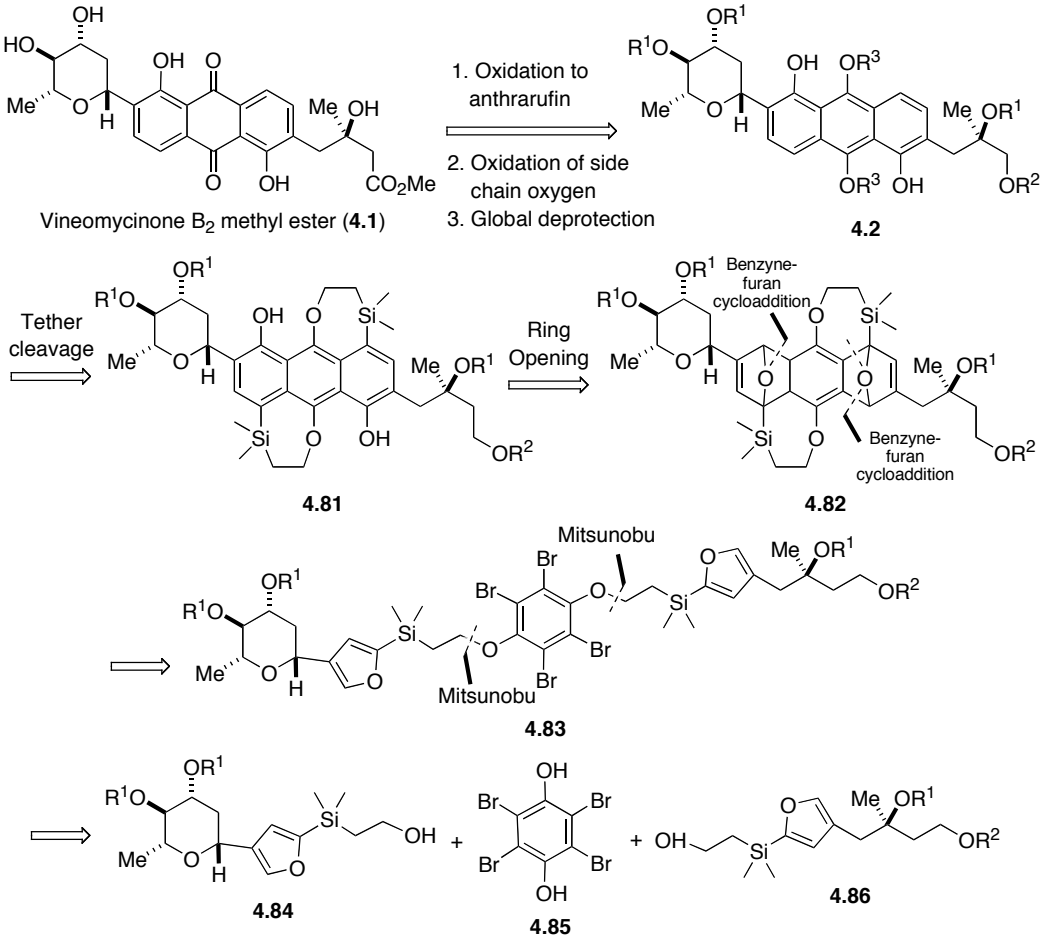
(Eq 4.3)

4.2 SECOND GENERATION APPROACH TOWARD VINEOMYCINONE B_2 METHYL ESTER

Our first approach encountered difficulties associated with the challenge of the tether cleavage and ring opening of bisoxabenzonorbornadiene **4.76**. After I took over the project, I decided to ***reverse the sequence of ring opening and tether cleavage step***. Scheme 4.17 presented the second generation retrosynthetic analysis for preparing vineomycinone B_2 methyl ester. Vineomycinone B_2 methyl ester was derived from the same intermediate **4.2** as our first generation approach (see Scheme 4.17). It was envisioned that the bridgehead silyl group in oxabenzonorbornadiene **4.82** would direct the regioselective ring opening reaction to give anthracendiol **4.81**. The conversion of

4.81 into **4.2** required cleavage of carbon-silicon bonds. It was anticipated that oxabenzonorbornadiene **4.82** could be derived from tetrabromide **4.83** *via* tandem benzyne-furan cycloadditions. Tetrabromide **4.83** would be prepared by the iterative Mitsunobu coupling of *p*-tetrabromohydroquinone **4.85** with the silicon-substituted furans **4.84** and **4.86**.

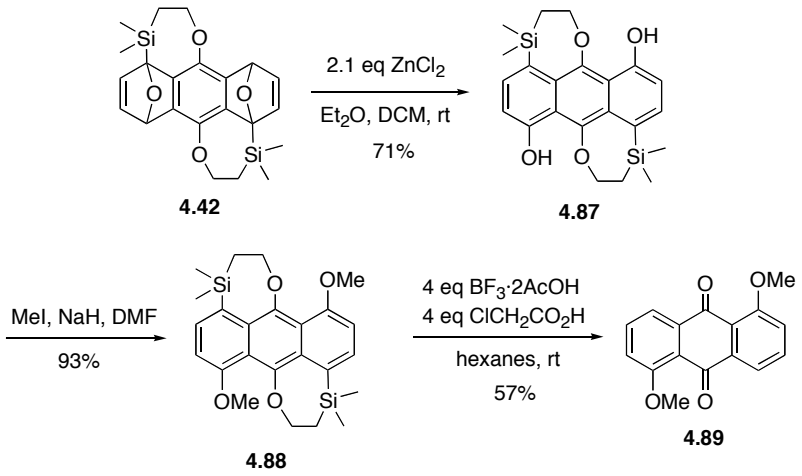
Scheme 4.17



Since bisoxabenzonorbornadiene **4.42** had been synthesized, we used this substrate as a model to test our new synthetic strategy. Towards that end, we first set to the task of determining whether we could convert **4.42** into anthrarufin **4.89** *via* ring

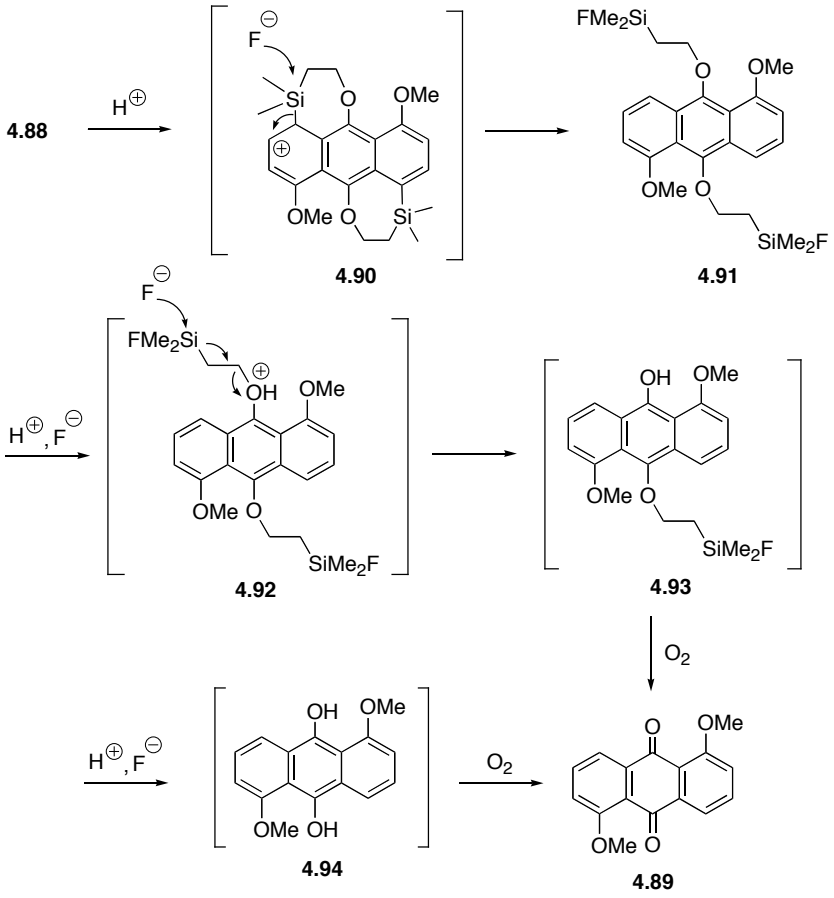
opening of bisoxabenzonorbornadiene rings followed by protiodesilylation and oxidation. In our early attempts, TMSOTf and 2,6-lutidine were examined for inducing the ring opening of **4.42**. However, only starting material was recovered, as well as some unidentified products. Ring opening of **4.42** with zinc chloride, which was advantageously employed by Kristen Procko in our group,[183] afforded a single regioisomeric anthracenediol **4.87** in 71% yield. Subsequent alkylation of **4.87** using methyl iodide and sodium hydride provided aryl ether **4.88** in 93% yield. Protiodesilylation of **4.88** with excess TBAF at 70 ºC and oxidation in air *in situ* gave anthrarufin **4.89**, albeit in only 22% yield. Alternatively, treatment of **4.88** with boron trifluoride·acetic acid complex and chloroacetic acid in hexane at room temperature gave **4.89** in 57% yield,[184] whereas the yields were lower using ether or EtOAc as solvent. Thus, conversion of bisoxabenzonorbornadiene **4.42** into anthrarufin **4.89** *via* ring opening followed by tether cleavage and oxidation was successfully achieved, giving support to our proposed synthetic strategy.

Scheme 4.18



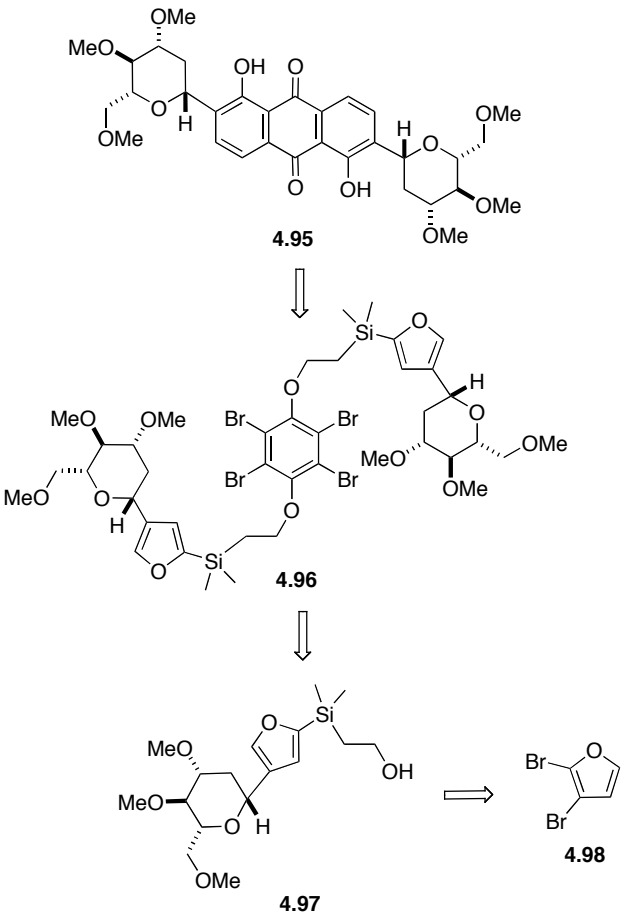
A possible mechanism for tether cleavage and oxidation of **4.88** is outlined in Scheme 4.19.[184] Protonation of the aromatic ring and subsequent nucleophilic attack of fluoride ion onto silicon generated intermediate **4.91**. Protonation of the oxygen in **4.91** led to oxonium ion intermediate **4.92**. A second nucleophilic addition of fluoride ion at silicon generated hydroquinone **4.93**, with release of difluorodimethylsilane and ethylene. Another nucleophilic addition of fluoride ion at silicon generated hydroquinone **4.94**. Oxidation of hydroquinones **4.93** and **4.94** in air resulted in the desired product **4.89**.

Scheme 4.19



With the success of the conversion of bisoxabenzonorbornadiene **4.42** to anthrarufin **4.89**, efforts were focused on the other model target **4.95** that contains two substituted *D*-glucoses symmetrically positioned on the anthrarufin (Scheme 4.20). There are two reasons that we considered to have *D*-gluose substituents on model **4.95**. First, vineomycinone B_2 methyl ester has an olivose linked to the anthrarufin core, and *D*-glucose is structurally similar to olivose. Second, the synthesis of *D*-glucose[185] is simple. We envisioned that anthrarufin **4.95** could arise from tandem benzyne-furan cycloadditions of tetrabromide **4.96** followed by ring opening, tether cleavage and oxidation. The tetrabromide **4.96** would be derived from furan **4.97** *via* Mistunobu couplings with tetrabromohydroquinone. Since some examples show that manipulation of 2,3-dibromofuran **(4.98)** would lead to a 2,4-disubstituted furan,[186] we decided to initiate the synthesis of furan **4.97** from **4.98**.

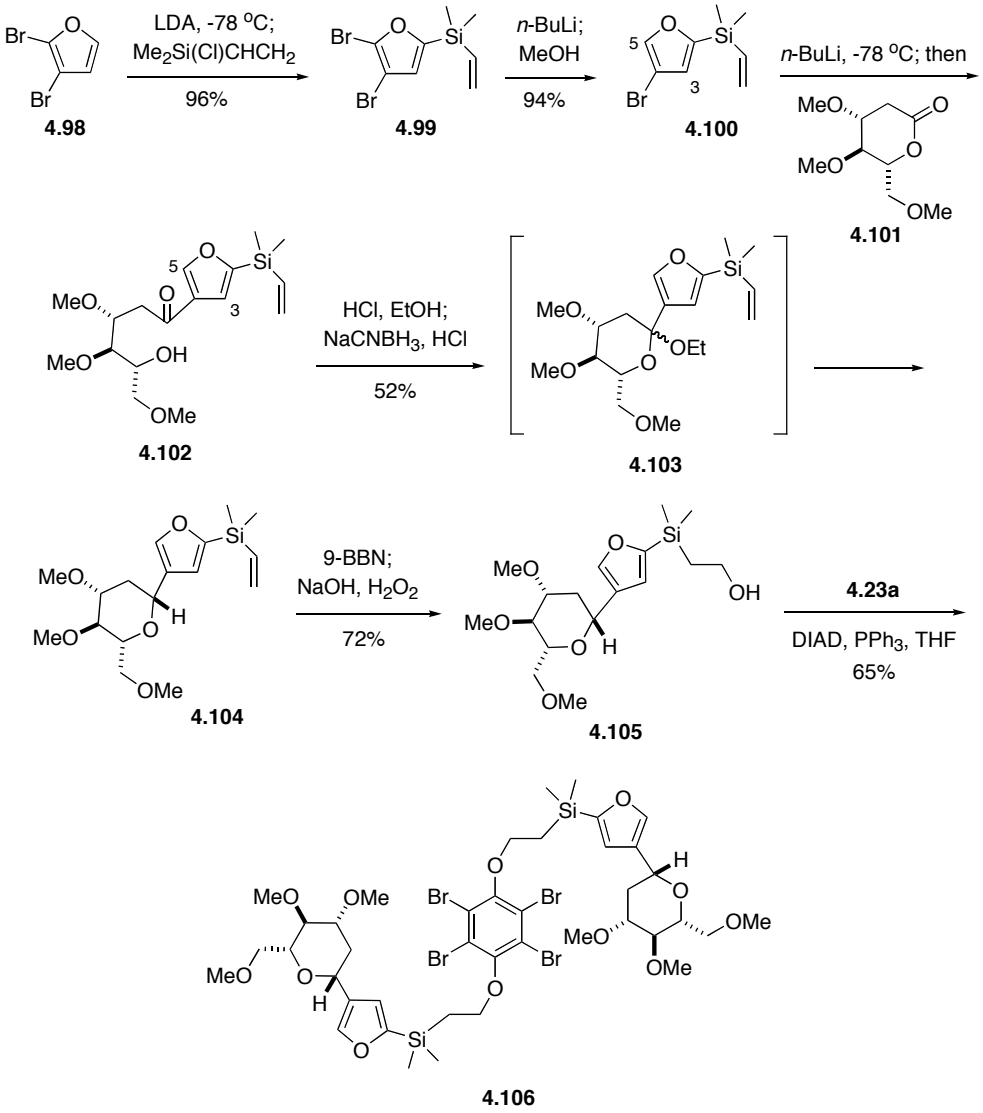
Scheme 4.20



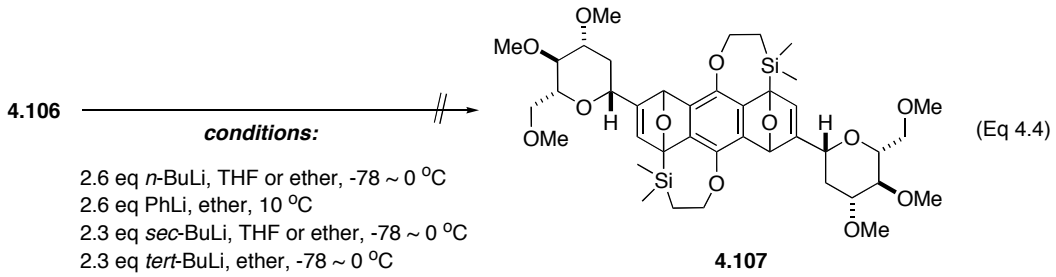
Lithiation of 2,3-dibromofuran (**4.98)** with LDA at low temperature followed by reaction with chlorodimethylvinylsilane gave dibromosilylfuran **4.99** (Scheme 4.21).[186] Metal-halogen exchange of **4.99** and subsequent quench with methanol gave monobromosilylfuran **4.100**. ^{1}H NMR spectrum of adduct **4.100** showed two singlets at 6.63 and 7.60 ppm, corresponding to the C3 and C5 protons of furan. Metal-halogen exchange again provided 4-lithiofuran intermediate, which was allowed to react with lactone **4.101** to afford ring opened hydroxy ketone **4.102** rather than ring closed lactols.[187,188] Evidence for the formation of **4.102** was supported by both IR, which showed a strong absorbance of carbonyl group at 1672 cm^{-1}, and ^{1}H NMR spectrum,

which showed a triplet at 3.04 ppm (J = 5.3 Hz), corresponding to methylene α to the ketone, and two singlets at 6.98 and 8.24 ppm, corresponding to C3 and C5 protons of furan at more down-field region. However, reduction of **4.102** with $NaCNBH_3$ in ethanolic HCl under Kaelin's conditions[187] failed to give the glucal substituted furan **4.104**. It was eventually found that treatment of hydroxy ketone **4.102** with ethanolic·HCl at room temperature furnished a mixture of ring closed ethyl acetal intermediates **4.103**, the ^1H NMR spectrum of which showed two singlets at 6.6 ppm and 7.5 ppm, corresponding to C3 and C5 protons of furan at up-field region. Subsequent reduction of **4.103** with $NaCNBH_4$ and ethanolic·HCl yielded the desired furan **4.104** in 52% yield. The yield decreased if the reduction was performed at higher temperature, with a higher concentration of acid catalyst, or for a longer period of time. In addition, no product was formed if $NaCNBH_3$ was added first followed by ethanolic·HCl. Furan **4.104** was then hydroborated employing 9-BBN and oxidized (NaOH, H_2O_2) to afford alcohol **4.105** in 76% yield. Mitsunobu coupling of alcohol **4.105** with *p*-tetrabromohydroquinone gave the cycloaddition presursor **4.106** in 65% yield.

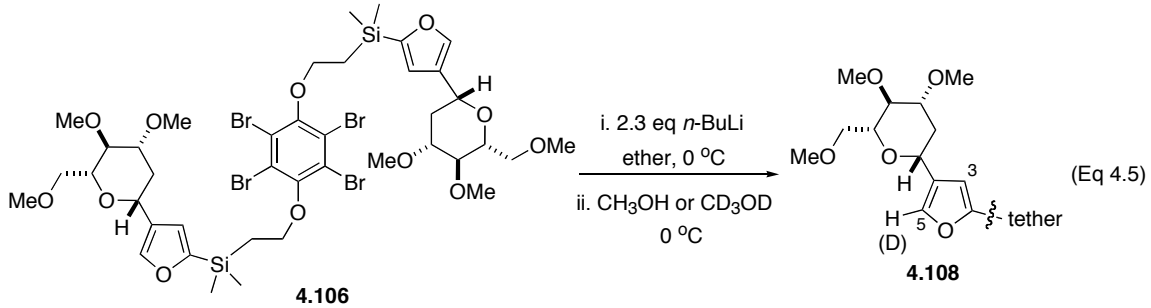
Scheme 4.21



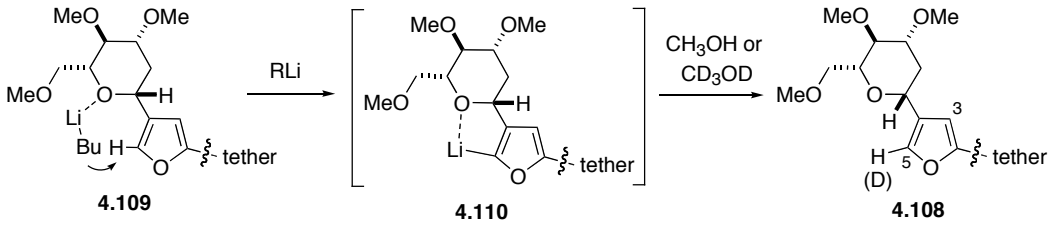
Tetrabromide **4.106** was then evaluated in the cylcoaddition reaction. Unfortunately, no significant quantities of biscycloadduct **4.107** were obtained upon treatment of **4.106** with alkyllithium reagents under a variety of conditions (lithium reagents: *n*-BuLi, *sec*-BuLi, *tert*-BuLi or PhLi; solvents: THF or Et_2O; temperatures: -78 ~ 0 °C) (Eq 4.4). In all cases, complex mixtures as well as recovered starting material **4.106** was obtained.



In order to understand the origin of the failure, we performed a deuterium-quenching experiment. In the event, a solution of *n*-BuLi (2.3 eq) was added dropwise to a solution of **4.106** in Et_2O at 0 °C (Eq 4.5). After stirring for 20 min, the reaction was quenched with CH_3OH. The appearance of C5 and C3 furan protons in ^{1}H-NMR indicated that the cycloaddition was not complete. In addition, integration of the furan protons in ^{1}H-NMR showed that the ratio of C5 proton to C3 proton was 1 : 1. However, a ratio of 1 : 2 was observed if the reaction was quenched with CD_3OD. The smaller ratio of C5 proton suggested that deprotonation of C5 proton by the lithium reagents had occurred. Presumably, the oxygen of the sugar directed *n*-BuLi to undergo deprotonation at C5 position of furan (Scheme 4.22). The resultant furyllithium **4.110** could be stabilized by the chelation of oxygen to form a 5-membered ring intermediate. Similar results were also observed under several conditions (*n*-BuLi or *sec*-BuLi in ether; 0 °C or -60 °C).



Scheme 4.22



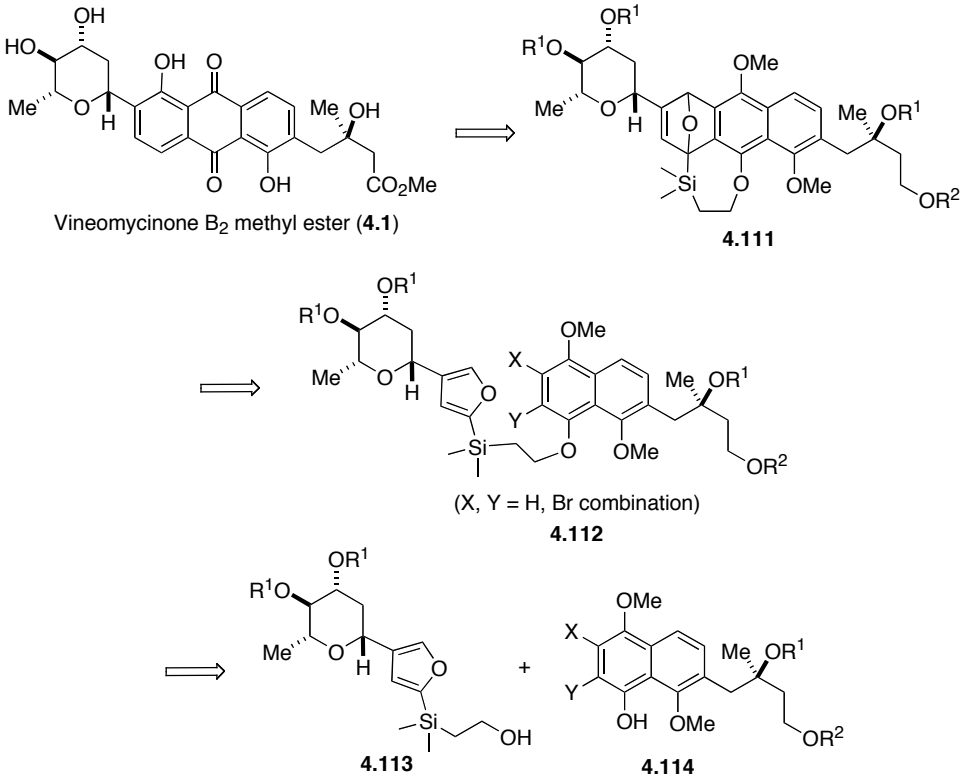
In summary, the conversion of bisoxabenzonorbornadiene **4.42** into anthrarufin **4.89** was achieved *via* ring opening followed by tether removal and oxidation. However, when we extended this strategy to a model **4.106** with substituted *D*-glucose, the benzyne-furan cycloaddition failed to give the cycloadduct **4.107**. Hence, this was a poor model. At this point, we decided to transfer our efforts to other possible naphthyne-furan cycloadditions for the construction of anthrarufin cores.

4.3 THIRD GENERATION APPROACH TOWARD VINEOMYCINONE B_2 METHYL ESTER

Both *o*-dibromonaphthalene and monobromonaphthalene derivatives have been reported as naphthyne precursors.[189] In general, generation of naphthyne intermediates from *o*-dibromonaphthalenes requires lithium reagents, whereas generation from monobromonaphthalenes needs amide bases. Initially, it was expected that bromonaphthalene **4.112** might be a suitable naphthyne-furan cycloaddition precursor (Scheme 4.23). At this point, the combination of X/Y was tentatively assumed to be Br/Br or H/Br. The naphthalene and furan moieties in **4.112** are linked by a two-carbon silicon tether, which allows for controlling the regiochemistry during cycloaddition process. Vineomycinone B_2 methyl ester is envisioned to arise from the cycloadduct **4.111** *via* ring opening of the oxabenzonorbornene, cleavage of the silicon tether, oxidation of the anthracene ring, global removal of the oxygen protecting groups, and

adjustment of the oxidation level of the side chain oxygen. Cycloadduct **4.111** could arise from intramolecular cycloaddition of bromonaphthalene **4.112** that in turn would be prepared *via* Mitsunobu coupling of furan **4.113** with naphthol **4.114**.[190]

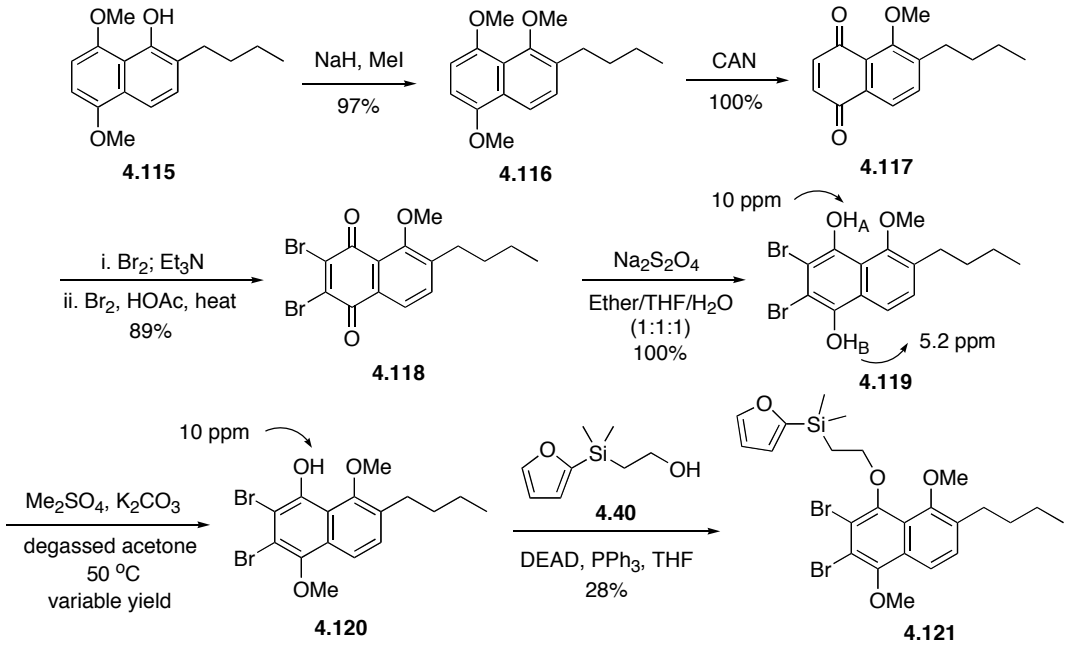
Scheme 4.23



In our model investigation directed toward evaluating the feasibility of the strategy set forth in Scheme 4.24, we were able to prepare *o*-dibromonaphthalene **4.121**, a naphthyne-furan cycloaddition precursor. Methylation of naphthol **4.115**[191] afforded trimethoxynaphthalene **4.116** in 97% yield, and the subsequent oxidation of **4.116** with CAN generated quinone **4.117** in quantitative yield. Bromination of **4.117** followed by reduction with $Na_2S_2O_4$ gave hydroquinone **4.119** in 89% yield over three steps.[192] Phenolic OH_A in **4.119** is more sterically hindered than OH_B. The ^1H NMR spectrum of

4.119 shows that H_A exhibits hydrogen bonding with the methoxy group (δ 10 ppm). Therefore, methylation of hydroquinone **4.119** under weakly basic conditions occurred preferentially at OH_B to provide naphthol **4.120**, albeit in variable yields. Performing the reaction in degassed acetone under a nitrogen atmosphere did not improve the yield, and this process was usually accompanied by oxidation to provide dibromoquinone **4.118** as the major product. Mitsunobu coupling of naphthol **4.120** with alcohol **4.40** furnished the cycloaddition precursor **4.121** in 28% yield together with a mixture of unidentified materials.

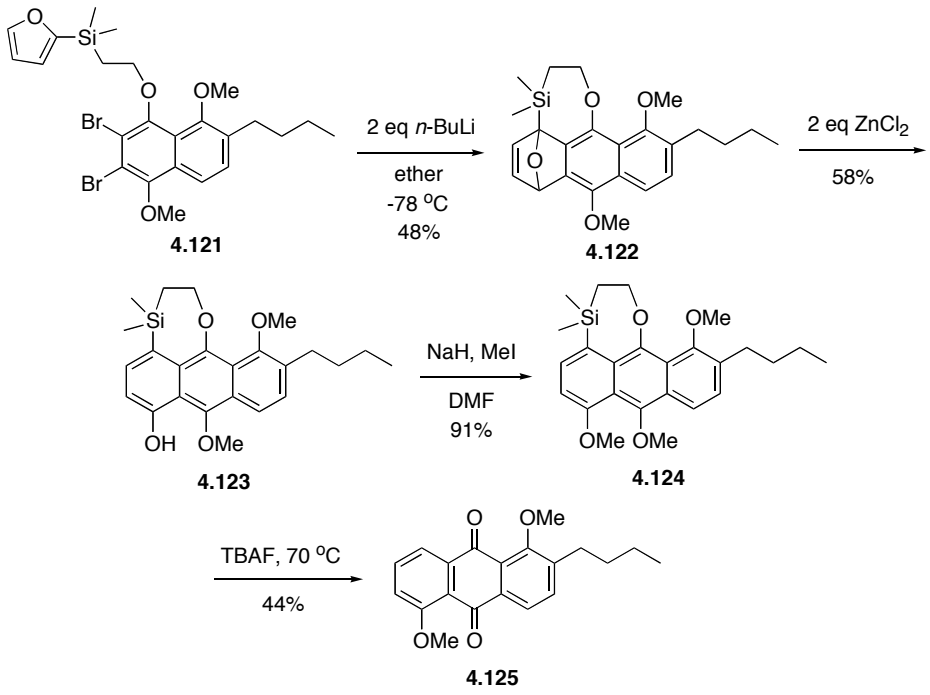
Scheme 4.24



Dibromonaphthol **4.121** was then examined in the cycloaddition reaction. Dropwise addition of *n*-BuLi (2.0 equiv) to a solution of **4.121** in ether at –78 °C gave the cycloadduct **4.112** in 48% yield (Scheme 4.25). However, changing the solvent from ether to THF or increasing the reaction temperature provided lower yield of **4.122**.

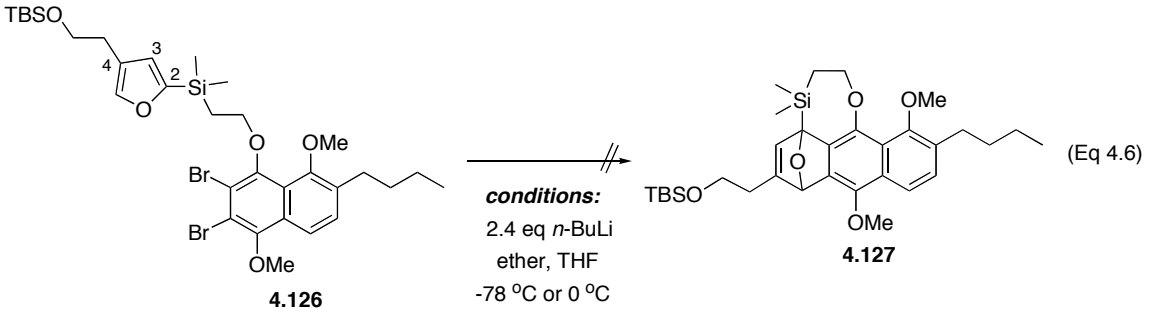
Treatment of cycloadduct **4.122** with $ZnCl_2$ afforded **4.123**, which underwent *O*-methylation to deliver trimethoxyanthracene **4.124** in 53% yield over two steps. Finally, treatment of **4.124** with TBAF followed by aerial oxidation gave anthrarufin **4.125** in 44% yield. This model study successfully demonstrated the promising naphthyne-furan cycloaddition for the synthesis of anthrarufin.

Scheme 4.25



Since vineomycinone B_2 methyl ester possesses two different side chains on the opposite positions of anthrarufin framework, we decided to examine the feasibility of the naphthyne-furan cycloaddition with precursor **4.126** in which the furan has a substituent at C4 position. Thus, substituted dibromonaphthalene **4.126** was prepared *via* Mitsunobu reaction of the naphthol **4.120** with the corresponding alcohol. Unfortunately, addition of *n*-BuLi to **4.120** in ether at -78 °C led to several unidentified products rather than the

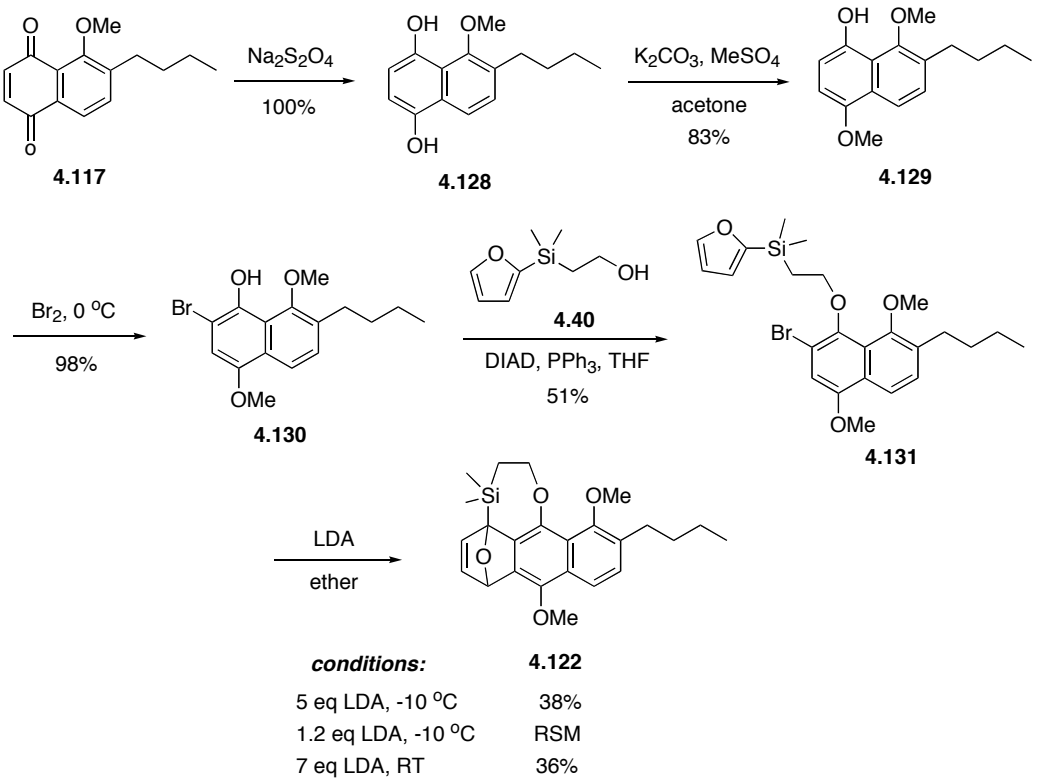
desired cycloadduct **4.127** (Eq 4.6). Attempts to induce the cycloaddition by increasing the temperature to 0 °C or using THF as solvent also failed to provide cycloadduct **4.127**.



It thus appeared that generation of a naphthyne *via* metal-halogen exchange of dibromonaphthalene **4.126** was problematic. At this stage, we decided to investigate the generation of naphthynes from monobromonaphthalenes. Deprotonation of monobromonaphthalenes with amide bases, such as LDA or Caubere's base ($NaNH_2$, *t*-BuONa complex) is known to generate naphthyne intermediates.[193] The use of amide bases may avoid some possible side reactions, including addition of *n*-BuLi to the oxabicyclic rings. Thus, we started the synthesis of model monobromonaphthalene **4.131**. Reduction of *p*-quinone **4.117** with $Na_2S_2O_4$ followed by selective *O*-methylation gave naphthol **4.129** in 93% yield over two steps (Scheme 4.27). Regioselective bromination of naphthol **4.129** provided *ortho*-bromonapthol **4.130** in 83% yield. Mitsunobu coupling of naphthol **4.130** with alcohol **4.40** then the afforded the substituted naphthalene **4.131** in 51% yield. If the Mistunobu reaction was performed in toluene or CH_2Cl_2, some inseparable impurities were formed. With **4.131** in hand, attempts to induce cycloadditions were undertaken. Addition of LDA to a solution of naphthalene **4.131** in THF at -10 °C only led to the recovered starting material. TMEDA was examined as an additive; however, the reaction provided the similar result. Raising the reaction temperature to room temperature led to a mixture of unidentified materials. Gratifyingly,

we found that cycloaddition occurred in ether at -10 °C. However, the reaction required the use of at least four equivalents of LDA to effect complete consumption of the starting material. Eventually, the cycloaddition was optimized to 38% yield upon addition of five equivalents of LDA to a solution of **4.131** in ether at –10 °C.

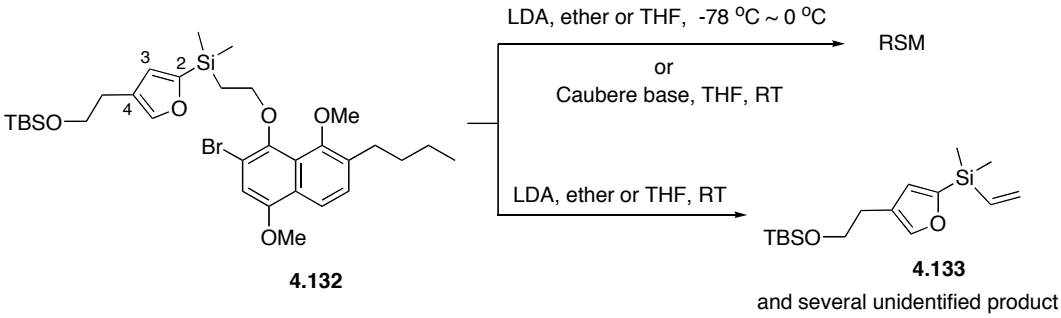
Scheme 4.26



Based on the success we had with the synthesis of cycloadduct **4.122**, efforts were directed to the model **4.132** with a substituent at C4 of the furan. Monobromonaphthalene **4.132** was prepared *via* a Mitsunobu coupling of bromonaphthalene **4.130** with the corresponding alcohol. LDA was added dropwise to a solution of **4.130** in THF or ether over 30 min at –78 °C, and the solution was allowed to warm to 0 °C over 1 h (Scheme 4.27). After aqueous workup, starting material **4.132** was recovered. A similar result was

obtained in an attempt using Caubere's base [194] to effect cycloaddition. These disappointing results led us to raise the reaction temperature. However, treatment of **4.132** with LDA in ether or THF at room temperature gave a mixture of the elimination product **4.133** along with several unidentified compounds. Since vinylsilane **4.133** has a high molecular weight, it is not volatile under the reduced pressure. Thus, we were able to identify it in the ^{1}H NMR spectrum, but we were not able to separate it from other side products.

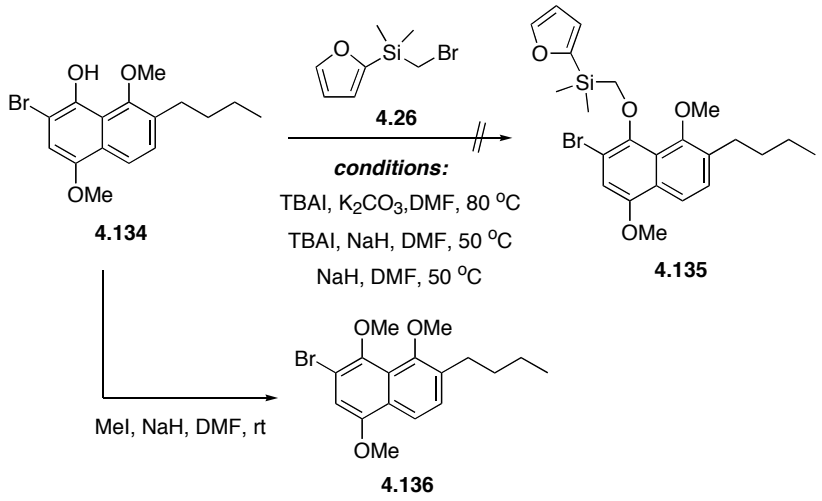
Scheme 4.27



The formation of **4.133** indicated the instability of the two-carbon tether substrate **4.132** toward LDA. In order to solve this problem, we decided to explore a substrate having one-carbon silicon tether, in which the elimination as shown in Scheme 4.27 might be avoided. The synthesis of bromonaphthalene **4.135** was thus undertaken. Treatment of bromonaphthalene **4.134** with TBAI, K_2CO_3 and **4.26** in DMF provided a mixture of unidentified materials rather than the alkylated naphthalene **4.135** (Scheme 4.28). When **4.134** and **4.26** were treated with NaH in DMF under various different conditions (room temperature, 50 °C, additive: TBAI), the reaction mainly provided the recovered **4.134**, and none of the desired **4.135** was isolated. However, when naphthol **4.134** was treated with NaH and MeI in DMF, alkylation occurred smoothly at room

temperature to give a clean naphthalene **4.136**. These results indicated that alkylation might be sensitive to steric effect.

Scheme 4.28



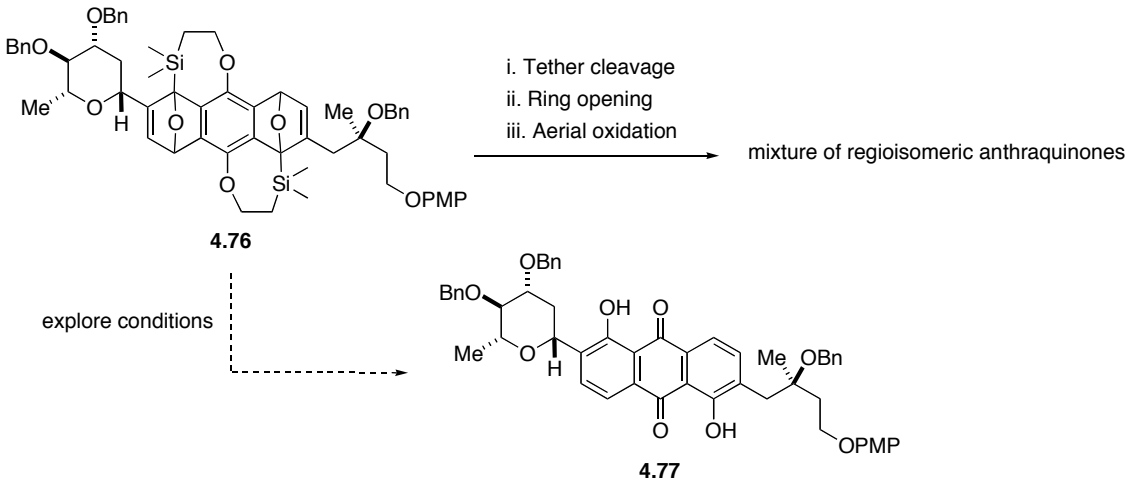
In summary, we have demonstrated the intramolecular naphthyne-furan cycloadditions using two different naphthyne precursors **4.121** and **4.131** to give cycloadduct **4.122**, which was converted into anthrarufin **4.125** through ring-opening, tether cleavage, and oxidation. However, extension of the cycloaddition to substrates **4.126** and **4.132** did not provide fruitful results. In some cases, side reactions dominated the cycloaddition process and might have been the reason for the failed reaction. At this point, we decided to revisit the first generation approach.

4.4 REVISITING THE FIRST GENERATION APPROACH

4.4.1 Model Systems

Our first generation approach to vineomycinone B_2 methyl ester had met the challenge in which the tether cleavage of bisoxabenzonorbornadiene **4.76** followed by ring opening reaction provided a mixture of isomeric anthraquinones (Scheme 4.29). If generating the mixture of anthraruquinones could be avoided, and significant amount of separable anthrarufin **4.77** could be obtained, the first generation approach to vineomycinone B_2 methyl ester should be successful. Potential conditions to cleave the silicon-carbon bonds and open bisoxabenzonorbornadiene rings were then explored.

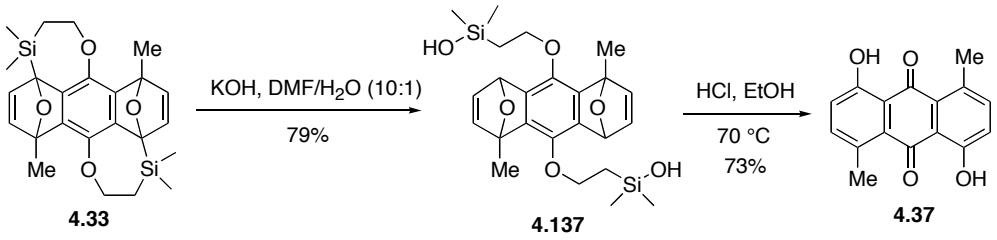
Scheme 4.29



Since Rickborn had reported that bridgehead TMS groups were efficiently cleaved using KOH or KO*t*-Bu in DMSO,[195] we decided to apply his conditions for the tether cleavage of bisoxabenzonorbornadiene **4.33**. Treatment of **4.33** under Rickborn's conditions afforded **4.137**, but the reaction was relatively slow and gave a dark solution. After extensive screening of various combinations of bases (KOH, NaOH, K_2CO_3) and solvents (DMSO, DMF, water), it was discovered that the use of KOH in DMF/H_2O

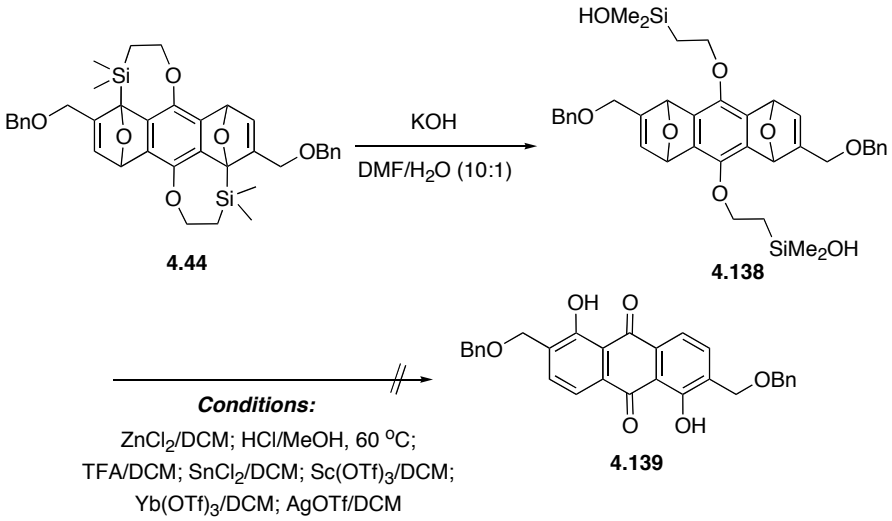
(10:1) was more effective, providing **4.137** in 79% yield (Scheme 4.30). Under the modified conditions, reaction was complete in two hours, and the solution retained a light yellow color. Ring opening of **4.137** with HCl in ethanol[196] and subsequent aerial oxidation *in situ* provided anthrarufin **4.37** in 73% yield.

Scheme 4.30



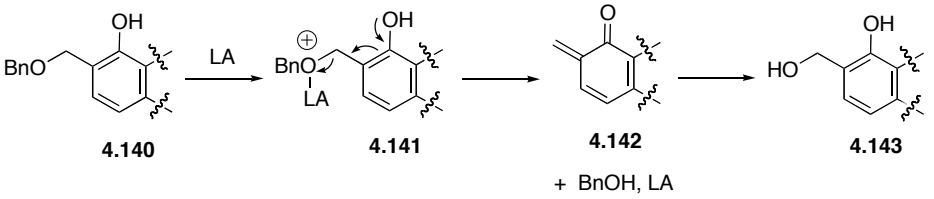
It was found that the modified Rickborn conditions were also capable of cleaving the bridgehead carbon-silicon bond of bisoxabenzonorbornadiene **4.44** to give **4.138** (Scheme 4.31). However, ring opening of **4.138** with $ZnCl_2$, HCl, TFA, $SnCl_2$, $Sc(OTf)_3$, $Yb(OTf)_3$, or AgOTf in air provided a mixture of unidentified materials, and no anthrarufin **4.139** was obtained.

Scheme 4.31

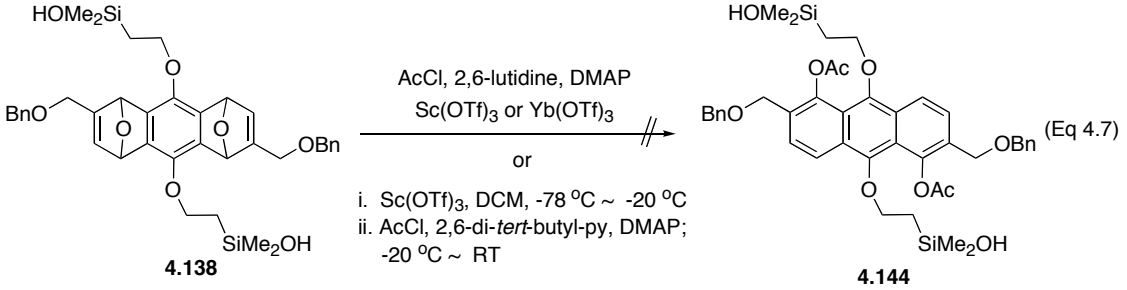


We reasoned that the anthrarufin **4.139** was not stable toward Lewis acids. A possible side reaction is shown in Scheme 4.32. Lewis acid-catalyzed elimination of a benzyl alcohol might provide an intermediate **4.142**. Addition of nucleophiles such as water or anions of acids and solvents, to **4.142** could generate phenol **4.143**. However, we do not have evidence for this side reaction.

Scheme 4.32

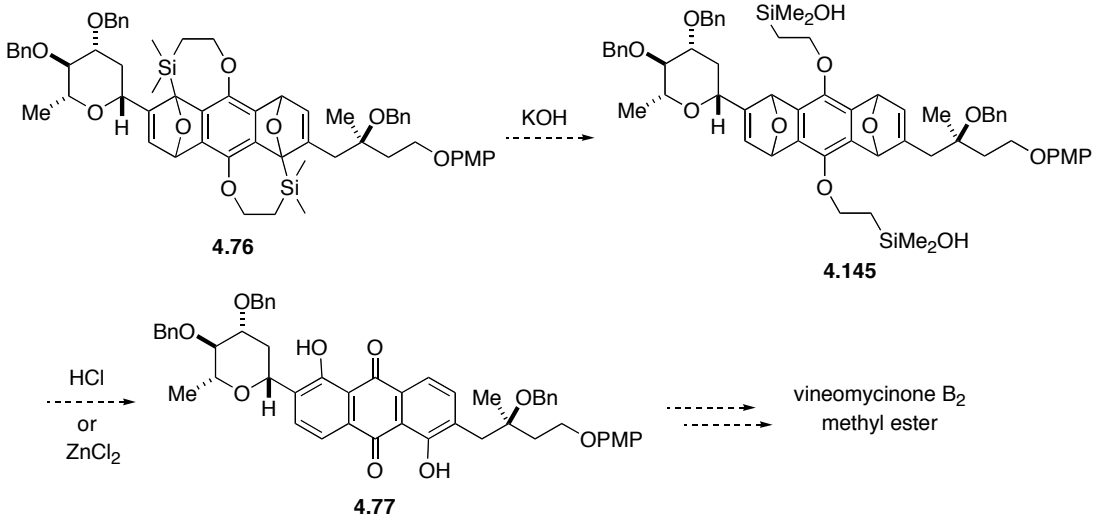


We then tried to open oxabicycle **4.138** and acylate the resultant phenol *in situ* to reduce the tendency of possible elimination associated with the electron-rich aromatic ring system. Unfortunately, treatment of oxabicycle **4.138** with $Sc(OTf)_3$ or $Yb(OTf)_3$ in the presence of AcCl, DMAP, and 2,6-lutidine led to recovered **4.138** (Eq 4.7). Presumably, the base completely suppresses the Lewis acidity of the metal salts. In a stepwise experiment, $Sc(OTf)_3$ was added to **4.138** in methylene chloride at –78 °C. The reaction was allowed to warm up to –20 °C, and then AcCl, DMAP, and 2,6-di-*tert*-butylpyridine were added, but only multiple polar materials were observed.



In summary, we were able to convert bisoxabenzonorbornadiene **4.33** to anthrarufin **4.37**, however, ring opening of **4.44** failed to provide **4.139**. It was assumed that benzyloxy group α to the aromatic ring would cause the instability of **4.139** toward Lewis acid. We believe that substrate **4.76** might not have this problem since it has different functionalities. Therefore, we decided to examine the newly discovered condition to effect tether cleavage and regioselective ring opening reaction of substrate **4.76** (Scheme 4.33).

Scheme 4.33

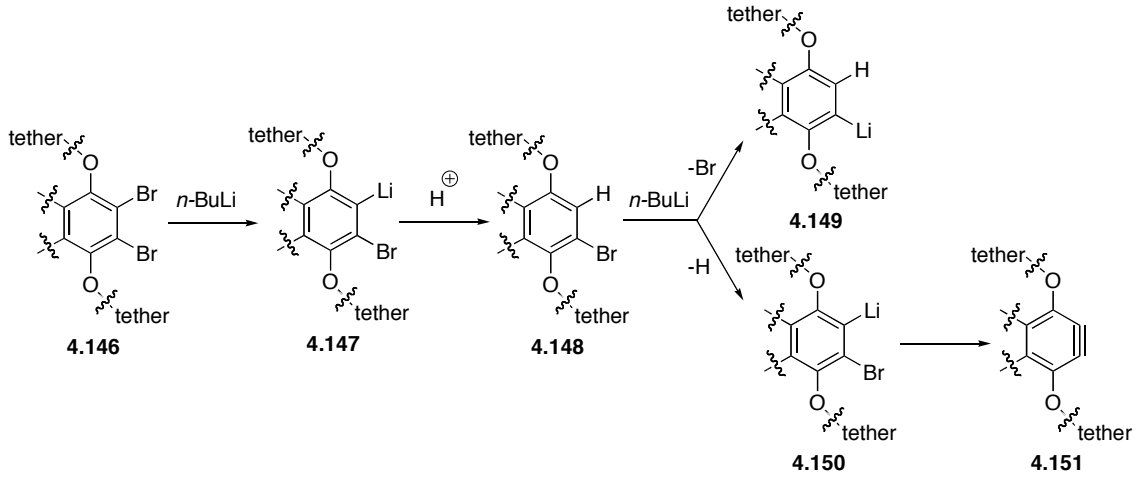


4.4.2 Synthesis of Vineomycinone B_2 Methyl Ester

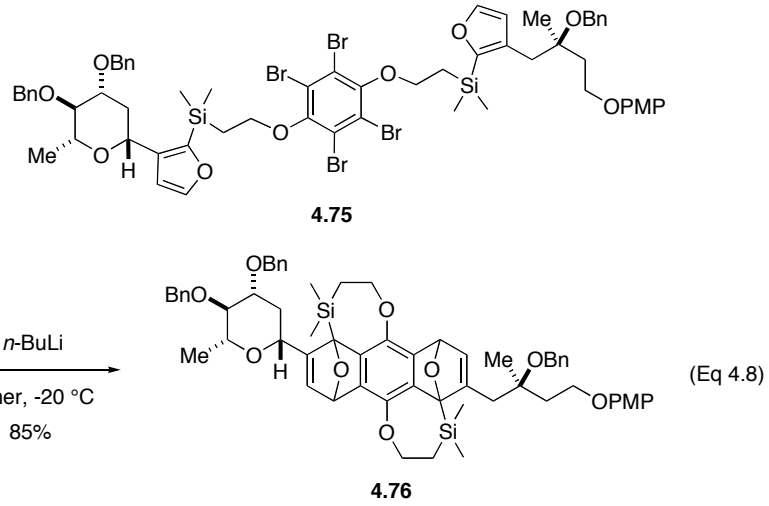
Prior to exploring the key tether cleavage and ring opening reaction shown in Scheme 4.33, we decided to optimize the cycloaddition with tetrabromide **4.75**. As shown in Eq 4.2, Sparks obtained cycloadduct **4.76** in variable yields (30-60%). The variable yields could arise from the "wet" tetrabromide materials, so that existing water may quench the aryllithium **4.147** derived from metal-bromide exchange to give **4.148** (Scheme 4.34). The benzyne generation requires deprotonation of bromide **4.148** to give

4.150. However, in the presence of excess *n*-BuLi, metal-halide exchange to give aryllithium **4.149** will be preferential compared to deprotonation reaction. Thus, generation of benzyne precursor **4.150** will meet problems.

Scheme 4.34



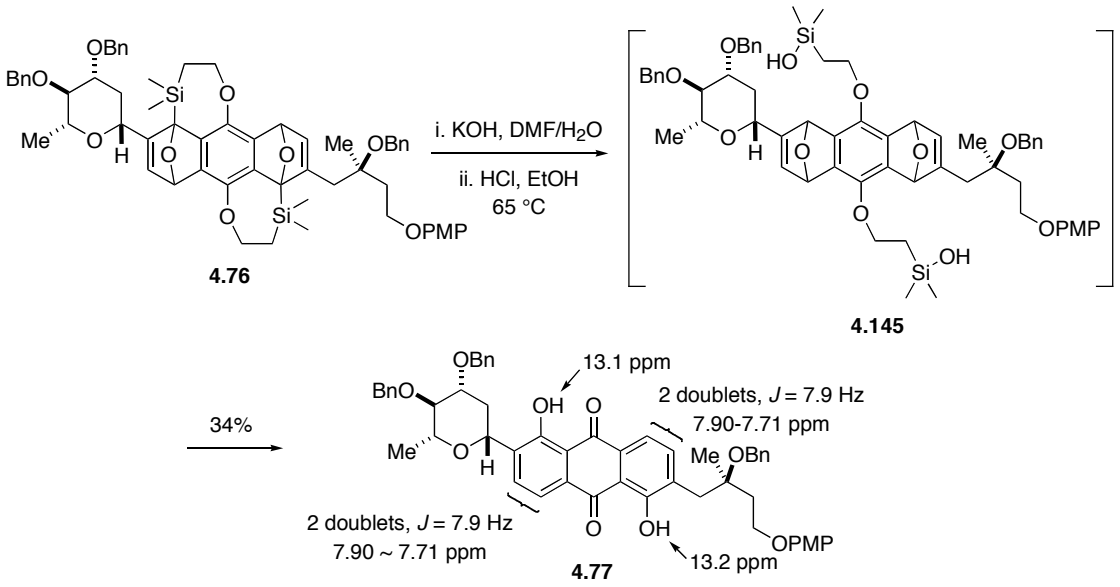
In order to optimize cycloaddition, I thought that removal of water from **4.75** might increase the yield of **4.76**. Benzyne precursor **4.75** was dried in a Kügelrohr oven under vacuum for two hour at 140 ºC. Dropwise addition of 3.0 equivalents of a dilute solution of *n*-BuLi (0.23 M) to a solution of dry tetrabromide **4.75** in Et_2O at –20 °C afforded diastereomeric mixture of product **4.76** in 85% yield (Eq 4.8). The reaction temperature is crucial to effect the efficiency of the cycloaddition. If cycloaddition proceeded at –78 °C or –50 °C under similar conditions, less than 30% yield of **4.76** was isolated as well as other unidentified mixtures. This temperature dependence could be due to the slow generation of benzyne intermediates at low temperatures or other possible side reactions associated with aryllithiums and benzynes, such as nuclophilic addition of lithium reagents to benzynes, ring opening bisoxabenzonorbornadienes by *n*-BuLi, ene reactions and [2 + 2] cycloadditions.[165,197]



(Eq 4.8)

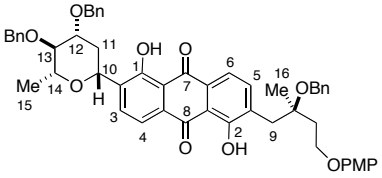
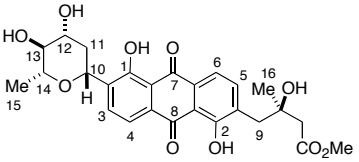
Cycloadduct **4.76** was then subjected to KOH in DMSO. The cleavage was slow, and the solution became dark. After examining different solvents, we found the reaction with KOH in DMF/H_2O (10:1) was faster and led to a clean mixture of diastereomers **4.145** (Scheme 4.35). Treatment of the resultant mixture thus obtained with Lewis acids to induce the ring opening reaction, such as $BF_3{\cdot}Et_2O/CH_2Cl_2$, $TiCl_4/CH_2Cl_2$ and EtOH/HCl/microwave, gave product **4.77** in less than 5% yield in combination with several unidentified baseline materials. The use of $ZnCl_2/CH_2Cl_2$ for the reaction provided **4.77** in 8% yield. Changing the Lewis acid to TFA generated **4.77** in about 7-20% yield. Eventually, we discovered that ring opening with hydrochloric acid in ethanol provided anthrarufin **4.77** in about 10-33% yield, and the yield of the reaction was dependent upon the concentration of HCl and reaction time. After extensively screening the concentration of HCl and reaction time, the desired anthrarufin **4.77** was reproducibly isolated in 34% overall yield.

Scheme 4.35



The regiochemical outcome of the ring opening and oxidation adduct **4.77** was verified by ^{1}H NMR spectrum, which showed four doublets (J = 7.9 Hz) at 7.90 ~ 7.71 ppm together with two singlets at 13.1 and 13.2 ppm, corresponding to the anthrarufinic and phenolic protons of vineomycinone B_2 methyl ester (Table 4.1).

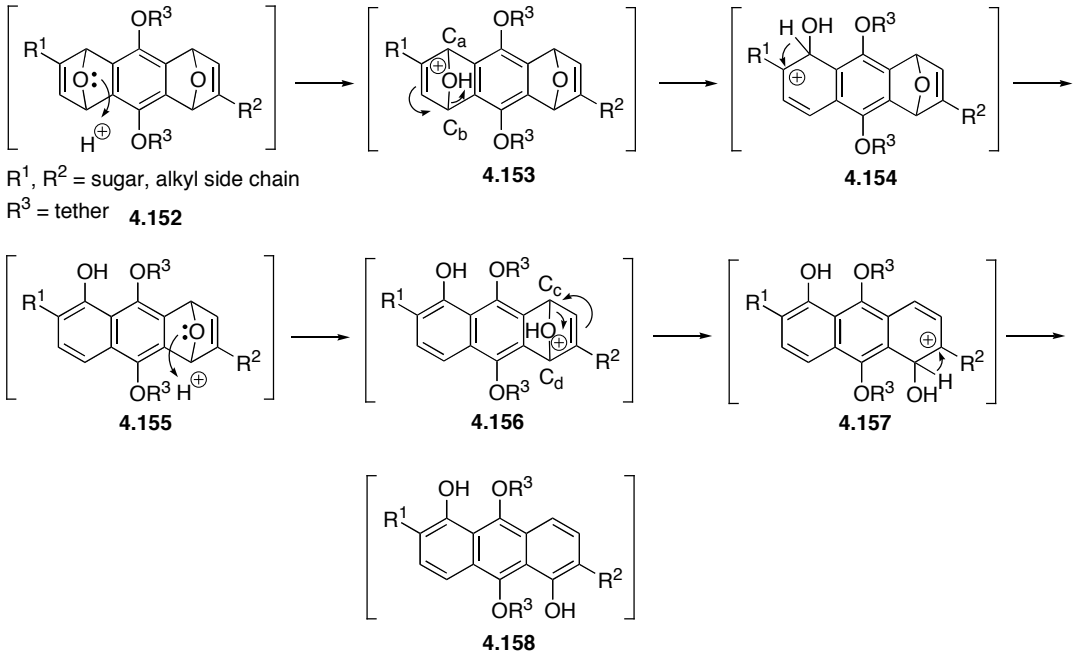
Table 4.1 ^{1}H NMR chemical shift data of compound **4.77** and **4.1**

^{1}H–NMR δ (ppm)	 **4.77**: δc	 Literature (Suzuki) **4.1**: δc[143f]
C1-OH & C2-OH	13.2 (s) 13.1 (s)	13.2 (s) 13.1 (s)
C3-H, C4-H, C5-H & C6-H	7.90 (d, *J* = 7.91 Hz); 7.85 (d, *J* = 7.91 Hz); 7.74 (d, *J* = 7.78 Hz); 7.71 (d, *J* = 7.91 Hz);	7.91 (d, *J* = 7.9 Hz) 7.85 (d, *J* = 7.9 Hz) 7.80 (d, *J* = 7.9 Hz) 7.69 (d, *J* = 7.9 Hz)
C9-H	3.19 (d, *J* = 13.6 Hz) 3.11 (d, *J* = 13.6 Hz)	3.11 (d, *J* = 13.6 Hz) 3.02 (d, *J* = 13.6 Hz)
C10-H	4.86 (dd, *J* = 11.5, 1.7 Hz)	4.94 (dd, *J* = 11.2, 1.8 Hz)
C11-H	2.69 (ddd, *J* = 12.8, 4.7, 1.7 Hz) 1.48-1.39 (m)	2.54 (ddd, *J* = 12.8, 4.9, 1.8 Hz) 1.48 (ddd, *J* = 12.8, 11.2, 11.2 Hz)
C12-H	3.85 (ddd, *J* = 13.5, 8.9, 4.7 Hz)	3.86 (ddd, *J* = 11.2, 9.0, 4.9 Hz)
C13-H	3.21 (t, *J* = 8.9 Hz, C23-H, 1 H)	3.22 (dd, *J* = 9.0, 9.0 Hz)
C14-H	3.57 (dq, *J* = 8.9, 6.2 Hz)	3.53 (dq, *J* = 9.0, 6.2 Hz)
C15-H	1.39 (d, *J* = 6.2 Hz)	1.42 (d, *J* = 6.2 Hz)
C16-H	1.34 (s)	1.31 (s)

The regioselective ring opening reaction was directed by substituents on oxabenzonorbornadienes. A plausible mechanism for the HCl-catalyzed ring opening process was shown in Scheme 4.36. Under the acidic condition, the O-C_b bond in **4.153** was expected to be cleaved preferentially to generate a more stable tertiary cation **4.154**, whereas O-C_a bond cleavage would only give a secondary cation. Aromatization of **4.154**

would provide **4.155**. Again, acid-catalyzed rearrangement would preferentially provide a tertiary cation **4.157** *via* O-C_c bond cleavage, while O-C_d bond cleavage would yield a secondary cation. Aromatization of **4.157** led to anthracenediol **4.158**.

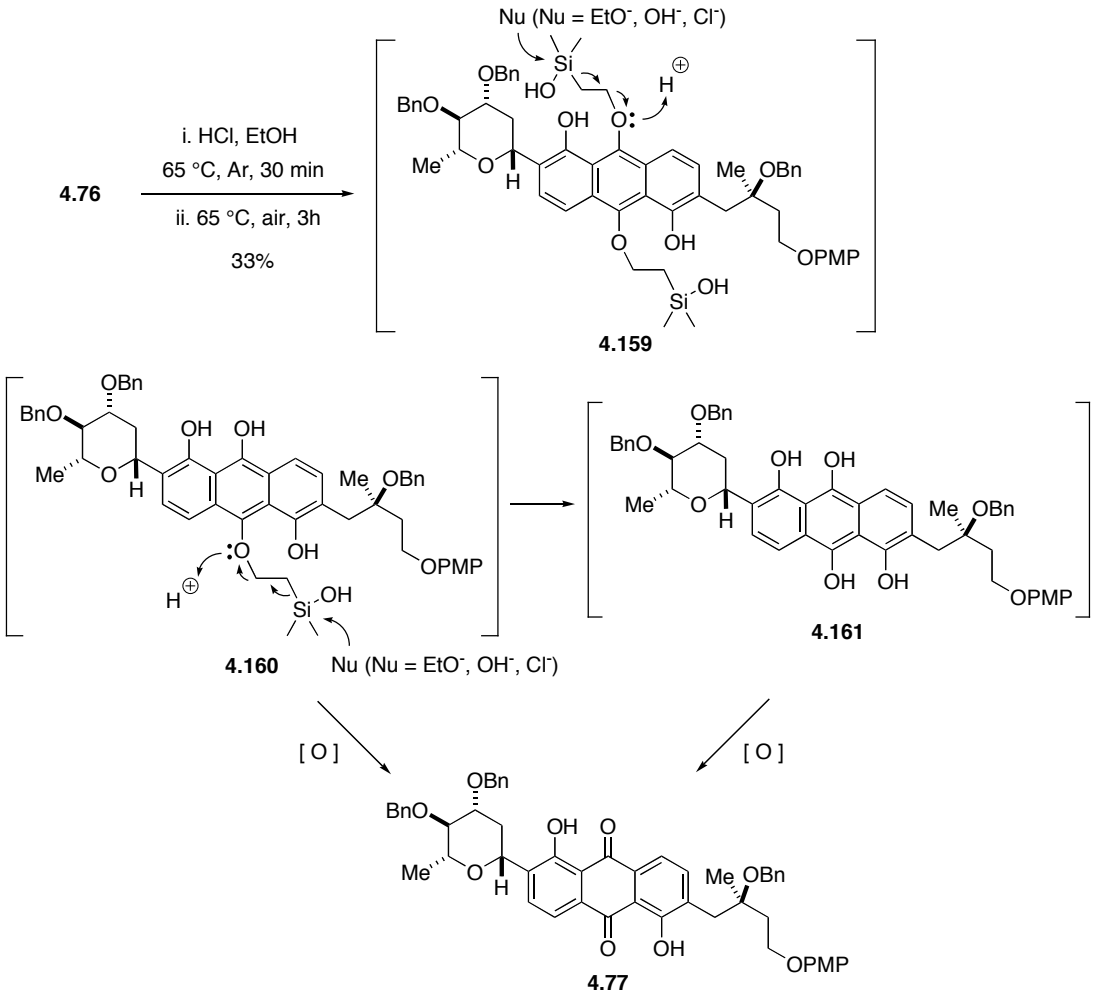
Scheme 4.36



The ring opening and oxidation process for the formation of anthrarufin **4.77** was studied. HCl was added to a solution of intermediate **4.76** in ethanol under argon (Scheme 4.37). The mixture was stirred for 30 min at 65 °C and then concentrated under reduced pressure. The crude ^{1}H NMR spectrum showed the presence of phenolic protons at 10.4 ppm[198] and absence of bridgehead protons of **4.76** at 5.7 ppm, which is the evidence for the formation of ring opened adduct **4.159**, or related intermediates **4.160**-**4.161** derived from acid-catalyzed cleavage of silicon tethers. The crude mixtures were then dissolved in ethanol and HCl was added. The reaction was stirred for 3 h at 65 °C in air, which resulted in the formation of anthrarufin **4.77** in 33% overall yield, likely *via*

aerial oxidation of intermediate **4.159**, **4.160**, and/or **4.161**. However, the reaction failed to give **4.77** if the reaction proceeded under the argon atmosphere or in the absence of HCl.

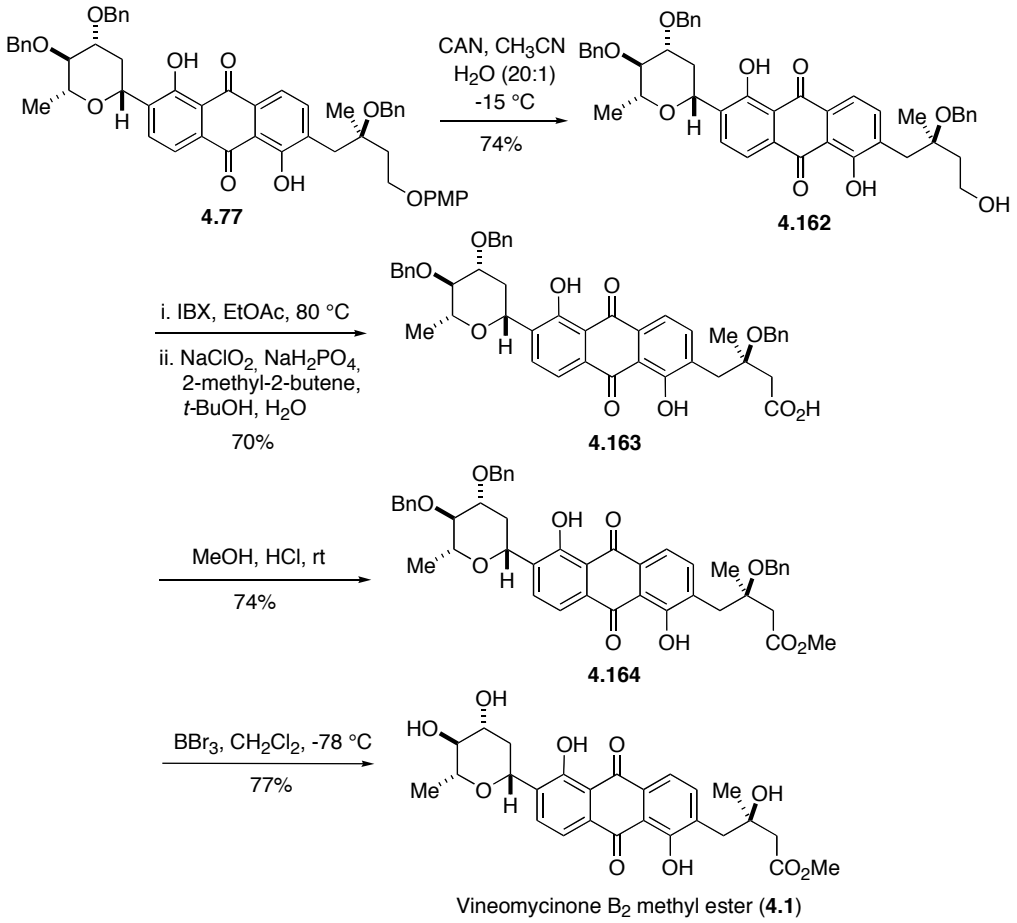
Scheme 4.37



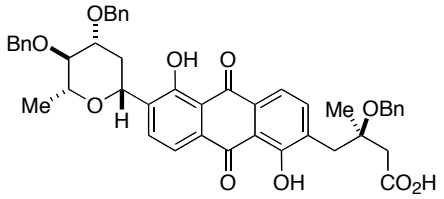
Completion of the synthesis of vineomycinone B_2 methyl ester (**4.1**) then required removal of the PMP and benzyl protecting groups, and adjustment of the oxidation level of the aliphatic side chain oxygen. The PMP group was oxidatively cleaved with CAN (20:1 acetonitrile/H_2O, –15 °C) to give alcohol **4.162** in 74% yield (Scheme 4.38), but the

yields were lower using typical solvent systems (1:1 DCM/H_2O, 4:1 acetonitrile/H_2O, 3:1:1 acetonitrile/pyridine/H_2O). Subsequent oxidation of alcohol **4.162** with PDC in DMF led to a low yield of acid **4.163** in combination with recovered **4.162**. Treatment of alcohol **4.162** with IBX generated an aldehyde intermediate,[199] which was transformed to acid **4.163** with $NaClO_2$ in 70% overall yield. Acid **4.163** was converted to its methyl ester **4.164** in 74% yield by treatment with HCl in methanol. Hydrogenolysis of **4.164** with Pd/C or $Pd(OH)_2$/C at hydrogen pressure up to 9 atm did not completely remove all of the benzyl groups. Attempted removal of the benzyl ethers with DDQ led to recovered starting material. Eventually, we found that deprotection of benzyl groups with BBr_3 in dichloromethane at –78 ^oC led to vineomycinone B_2 methyl ester (**4.1**) in 77% yield.

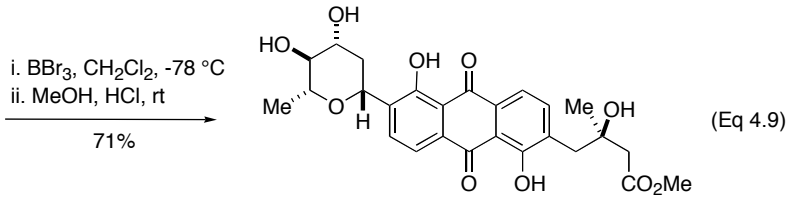
Scheme 4.38



Alternatively, global deprotection of the benzyl groups of the acid **4.163** with BBr_3 followed by work-up with methanolic HCl provided synthetic vineomycinone B_2 methyl ester (**4.1**) in 71% yield (Eq 4.9). The synthetic material obtained gave ^1H and ^{13}C NMR spectra identical to those of an authentic sample provided by Professor Marcus A. Tius (Table 4.2), and it exhibited an optical rotation ($[\alpha]^{24}_D$ +109.8, c 0.00091 in $CDCl_3$; lit.[143b] $[\alpha]_D$ +109.1, c 0.00066 in $CDCl_3$) and melting point identical to those reported in the literature (mp 183-184 °C; lit.[143d] mp 183-184 °C).



4.163



Vineomycinone B_2 methyl ester (**4.1**)

(Eq 4.9)

Table 4.2 ^{13}C NMR chemical shift of synthetic and authentic 4.1

Synthetic Sample: δ_c [a]	Authentic Sample (Tius): δ_c [a]	Literature (Suzuki): δ_c [143f]
188.2	188.2	188.2
188.2	188.2	188.1
173.3	173.3	173.3
161.4	161.4	161.3
159.0	159.0	159.0
139.6	139.6	139.6
138.3	138.3	138.3
134.7	134.7	134.7
133.3	133.3	133.3
131.9	131.9	131.84
131.8	131.8	131.78
119.4	119.4	119.4
118.9	118.9	118.9
115.6	115.6	115.6
115.5	115.5	115.5
78.1	78.1	78.0
75.9	75.9	75.9
73.1	73.1	73.1
71.8	71.8	71.8
71.3	71.3	71.3
51.7	51.7	51.8
44.4	44.4	44.4
40.5	40.5	40.5
39.4	39.4	39.4
27.3	27.3	27.3
18.1	18.1	18.1

[a] ^{13}C NMR spectra of synthetic and Tius' samples were recorded on the same Varian 500 MHz spectrometer at the University of Texas at Austin.

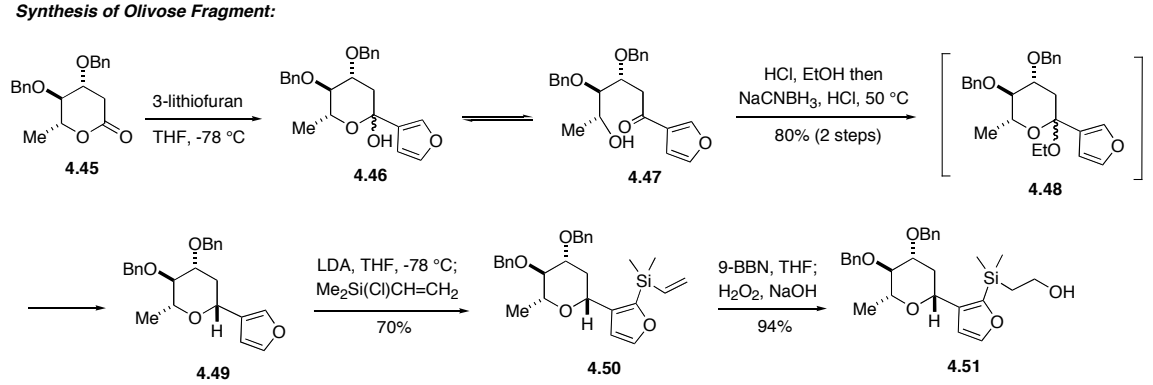
4.5 CONCLUSION

Vineomycinone B_2 methyl ester (**4.1**) possesses an olivose residue and a hydroxyisovaleryl side chain on the opposite position of anthrarufin, and a major challenge associated with its synthesis is to install these substituents regioselectively. Three generation approaches that feature double benzyne–furan cycloadditions and naphthyne–furan cycloadditions were studied toward vineomycinone B_2 methyl ester. The first generation approach was considered to be a more reliable one, whereas the second and third generation approaches only succeeded with the simple model substrates. In the model studies, furans and the reacting benzynes or naphthynes were linked with silicon tethers to give oxabenzonorbornadienes and, thus, the regiochemistry of Diels–Alder reactions could be controlled. Two different tactics for converting the intermediate oxabenzonorbornadienes to substituted anthrarufins were demonstrated. The first method entails the initial cleavage of the silicon tethers followed by regioselective ring opening of the oxabenzonorbornadienes and oxidation of the central ring giving the target anthrarufin, whereas the second features the regioselective ring opening of the oxabenzonorbornadienes followed by protiodesilylation and oxidation.

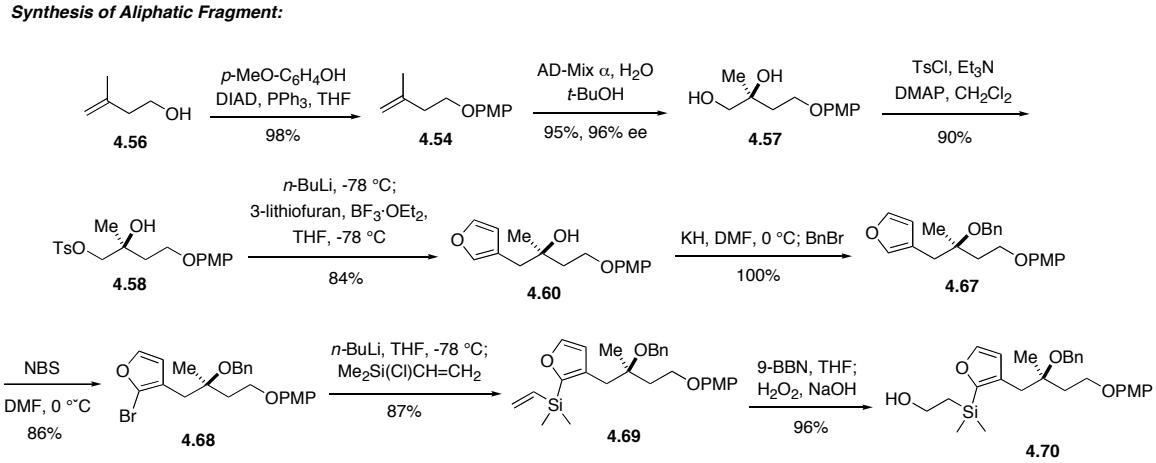
Using the chemistry demonstrated in the double benzyne-furan cycloaddition models, a novel and highly convergent synthesis of vineomycinone B_2 methyl ester has been completed by a process that required a total of 27 steps, with 0.17% overall yield from commercially available materials. The longest linear sequence required 16 steps and proceeded in 2.9% overall yield. The outline of the synthesis is shown in Scheme 4.39, 4.40 and 4.41. The synthesis features the first application of using silicon tethers as disposable linkers to control the regiochemistry in Diels–Alder reactions of substituted benzynes and furans for the total synthesis of *C*-aryl glycoside natural products. The tandem benzyne-furan cycloadditions provided access to the anthrarufin framework of

vineomycinone B_2 methyl ester, which contains olivose residue and aliphatic side chain at C2 and C6 positions, respectively. Manipulations of Diels-Alder adducts easily led to the synthetic vineomycinone B_2 methyl ester. This strategy enables the rapid assembly of the glycosyl-substituted aromatic frameworks of complex *C*-aryl glycoside antibiotics from simple starting materials.

Scheme 4.39

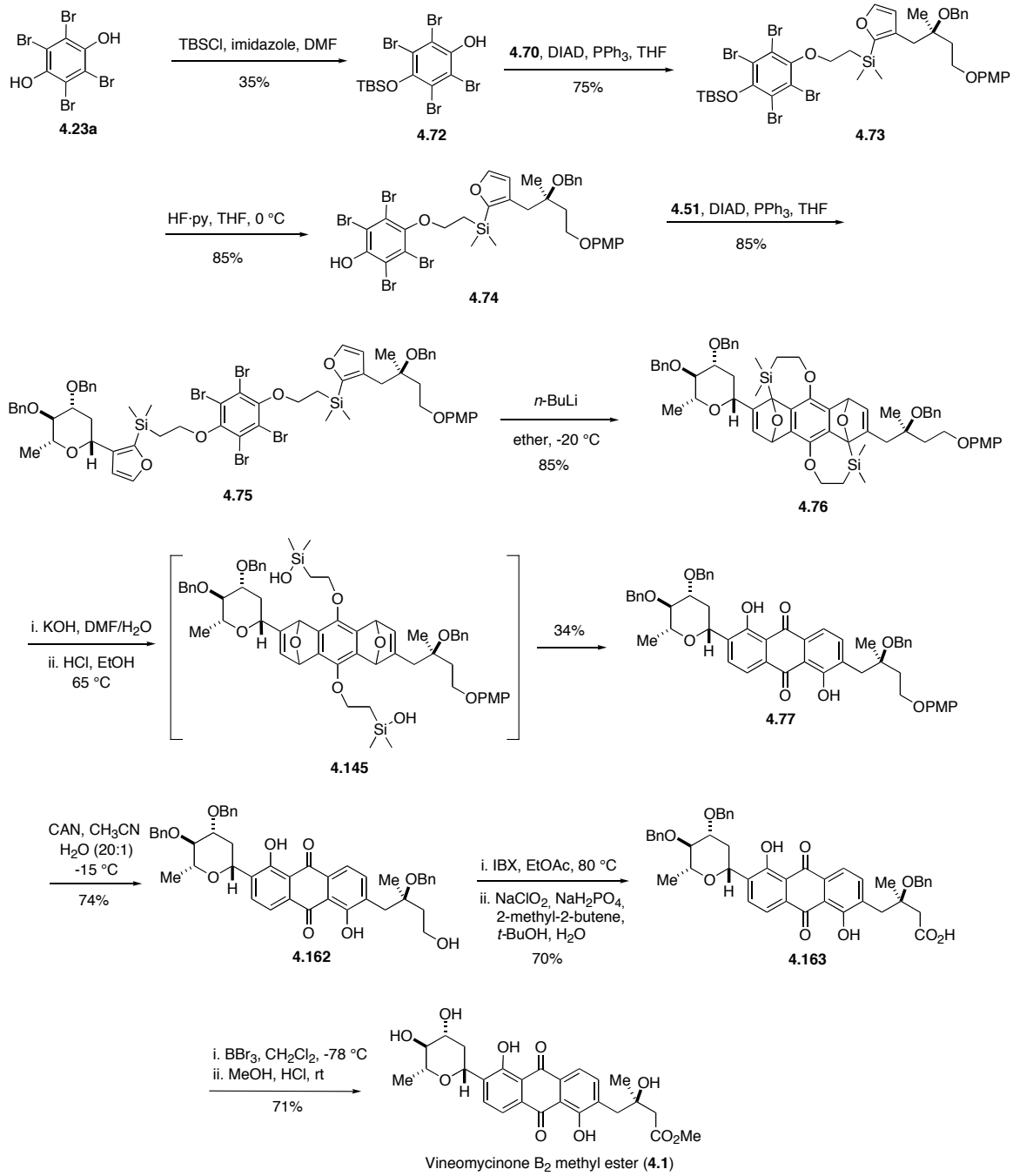


Scheme 4.40



Scheme 4.41

Synthesis of Vineomycinone B_2 Methyl Ester (4.1)



Chapter 5. Study toward the Synthesis of Actinophyllic Acid

5.1 Biological Activity and Structure of Actinophyllic Acid

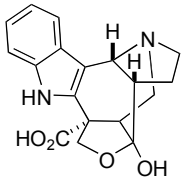
Fibrinolysis is an enzymatic cascade reaction that results in the degradation of fibrin by plasmin. Because of this process, small blood clots can be removed from circulation in the body. When plasmin degradation of fibrin exposes carboxy-terminal lysine residues, it causes the cleavage of plasminogen to generate plasmin. This process is encouraged by two plasminogen activators, tissue-type plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). When plasminogen is bound to fibrin, this cleavage process is more highly activated. Thus, the initial exposure of fibrin to plasmin accelerates fibrinolysis through positive feedback.[200]

Carboxypeptidase U (CPU) is one of the endogenous inhibitors to fibrinolysis. During coagulation and fibrinolysis, CPU is produced from its precursor proCPU by the action of proteolytic enzymes, such as thrombin, thrombin-thrombomodulin complex, or plasmin. CPU cleaves basic amino acids at the carboxy-terminal of fibrin fragments, which results in the loss of carboxy-terminal lysines. The resultant lysine binding sites serve to inhibit fibrinolysis. Thus, effective fibrinolysis can be achieved by inhibiting these lysine binding sites or CPU.

During a search for novel natural products for the discovery of therapeutic agents to treat cardiovascular disorders, 40000 extracts from Australian plants and marine organisms were tested with CPU/hippuricase, a coupled enzyme assay designed to discover CPU inhibitors.[201] The aqueous and methanolic extracts of the *Alstonia actinophylla* (A. Cunn.) K. Schum. were further investigated since they showed 100% inhibition at 50 mg/mL. Bioassay-guided fractionation led to the isolation of the CPU/hippuricase inhibitor actinophyllic acid (**5.1**), as a brown gum with $[\alpha]_D$ -29 (Figure

5.1).[202] The structure was determined from detailed 2D NMR studies.[202] Although over 250 alkaloid natural products have been isolated from species of *Alstonia* to date,[203] actinophyllic acid represents a new skeleton: 2,3,6,7,9,13c-hexahydro-1*H*-1,7,8-(methanetriyloxyme thano)pyrrolo [1´,2´:1,2]azocino[4,3-*b*]indole-8(5*H*)-car-boxylic acid.

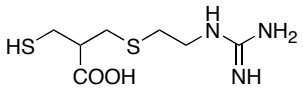
Figure 5.1



Actinophyllic acid (**5.1**)

Use of actinophyllic acid in a CPU/hippuricase coupled enzyme assay showed inhibition with an IC_{50} of 0.84 mM, compared to the known carboxypeptidase inhibitor, plummers inhibitor (**5.2**) (Figure 5.2), which had an IC_{50} of 6.4 mM. CPU catalyzes the hydrolysis of 4-hydroxyhippurylarginine to 4-hydroxyhippuric acid, while hippuricase promotes the trasformation of 4-hydroxyhippuric acid to 4-hydroxybenzoic acid. Despite its potency, the detailed mechanism of inhibition by actinophyllic acid is not clear.

Figure 5.2



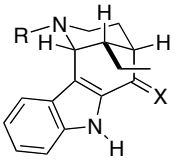
5.2

5.2 RETROSYNTHESIS OF ACTINOPHYLIC ACID AND SYNTHETIC METHODS

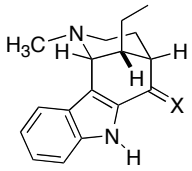
5.2.1 Retrosynthesis of Actinophylic Acid

Actinophyllic acid is an alkaloid containing a complex ring system that includes a quaternary chiral center and three tertiary chiral carbon atoms. In addition, it comprises an unusual tertiary amine attached to the α position of the C3 carbon atom of indole rather than the β position. Actinophyllic acid thus belongs to a family of 3-indolylamine natural products, including the uleine derivatives **5.3a**-**f**,[204] the epiuleine derivatives **5.4a**-**b**,[204] ervitsine derivatives **5.5a**-**b**,[205] BE 10988 (**5.6**),[206] which is a topoisomerase II inhibitor and exhibits anticancer activity, and dragmacidin D (**5.7**),[207] which is an antitumor agent (Figure 5.3). Our synthetic efforts were motivated by the combination of the challenging structure and the interesting biological properties. To date no synthesis of **5.1** has been reported.

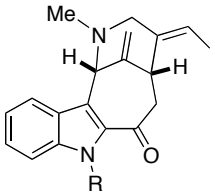
Figure 5.3



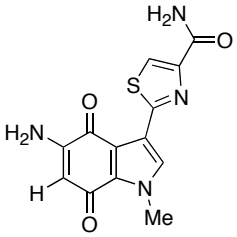
R	X	
CH_3	CH_2	Uleine (**5.3a**)
CH_3	O	Dasycarpidone (**5.3b**)
CH_3	α-OH, β-H	Dasycarpidol (**5.3c**)
H	O	Nordasycarpidone (**5.3d**)
H	CH_2	Noruleine (**5.3e**)
CH	α-CH_2OH, β-H	17-Hydroxydihydrouleine (**5.3f**)



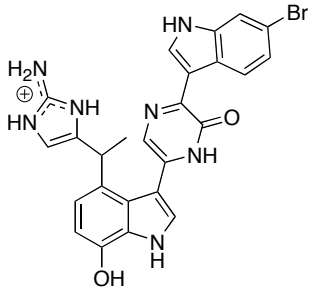
X = CH_2 20-Epiuleine (**5.4a**)
X = O 20-Epidasycarpidone (**5.4b**)



R = H, Ervitsine (**5.5a**)
R = Me, N_a-Methylervitsine (**5.5b**)



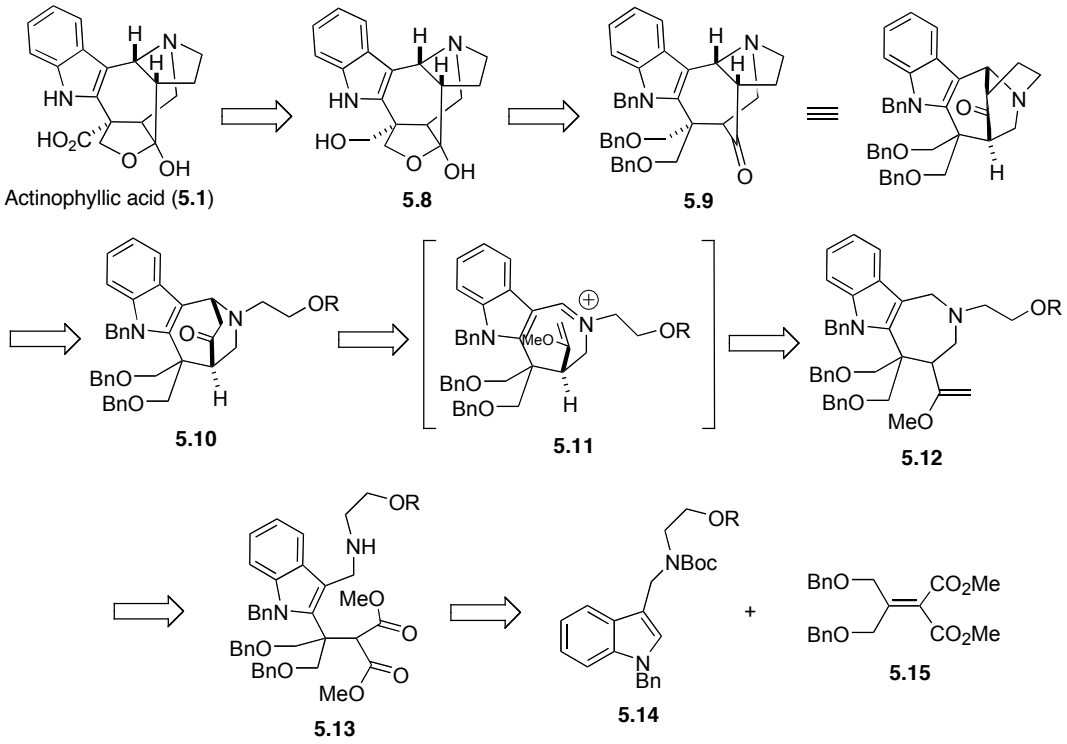
BE 10988 (**5.6**)



(±)-Dragmacidin D (**5.7**)

Since the most challenging feature of **5.1** is the complex ring system, it was felt that any successful synthesis would have to develop an efficient method for the construction of the ring system. We proposed that the use of a key oxidative Mannich reaction would provide the advantage of a high degree of convergency to access the core of actinophyllic acid. We envisioned that actinophyllic acid could arise from the oxidation of primary alcohol **5.8** that in turn could be prepared from **5.9** through removal of benzyl protecting groups (Scheme 5.1). The ketone **5.9** could be derived from bicyclic ketone **5.10** by intramolecular alkylation. The [3.2.2] bicyclic skeleton in **5.10** could be obtained from oxidative Mannich reaction of indole **5.12**. We expect that oxidation of indole **5.12** could generate the iminium ion intermediate **5.11** followed by reaction with the pendent vinyl ether to give bicyclic ketone **5.10**. The tertiary amine **5.12** would be derived from malonate **5.13** through lactam formation and a series of functional group manipulations. The malonate **5.13** could arise from the metal-catalyzed 1,4-addition of indole **5.14** to the α,β-unsaturated diester **5.15**.

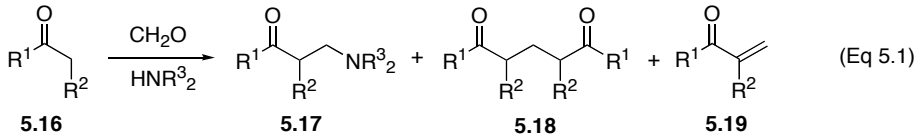
Scheme 5.1



5.2.2 Oxidative Mannich Reactions

A key step in our proposed synthesis of **5.1** is the oxidative Mannich reaction of **5.12**, so a brief review of such process is warranted. The Mannich reaction is an important carbon-carbon bond forming reaction in organic synthesis, and a variety of nitrogen-containing pharmaceutical and bioactive molecules are synthesized using this reaction.[208] There are, however, some inherent weak points of the traditional Mannich reaction.[209] For example, under more forcing conditions, epimerization of chiral centers sometimes occurs. Acid sensitive functional groups cannot survive, and unwanted side reactions might take place, such as the formation of methylene bisketone **5.18** and deamination product **5.19** (Eq 5.1).[210] Other problems associated with imines are

encountered when an electron-withdrawing protecting group is attached to the nitrogen atom of aliphatic imines. It is known that of aliphatic aldimines with enolizable α-protons are prone to isomerize to enamines, causing self-condensation with imines and giving poor yields of Mannich products. These limitations have led to the exploration of new synthetic methodologies under mild conditions.[208]

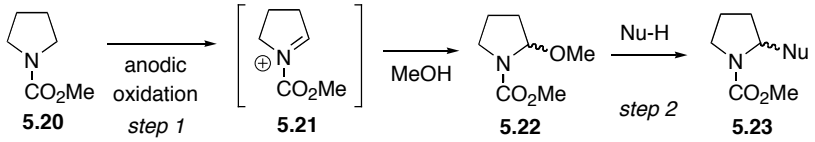


(Eq 5.1)

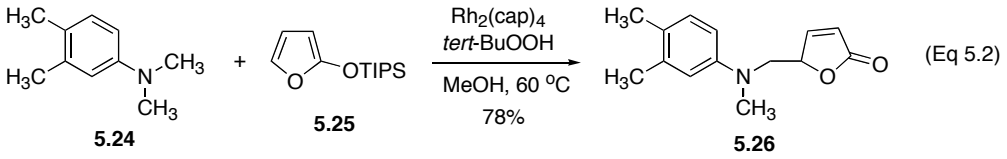
The oxidative Mannich reaction has received much attention in the past five years,[211] and it has extended the scope of the traditional Mannich reaction. The oxidative Mannich reaction involves oxidation of an amine to give an iminium ion followed by addition of a nucleophile to provide a new carbon-carbon bond. This process typically occurs under neutral and mild conditions, allowing for the presence of acid sensitive functional groups and protecting groups.[209] Epimerization of chiral centers can also be avoided.[212] Some examples show that oxidative Mannich reactions of *N*-carbobenzyloxy amines with malonates generate a new carbon-carbon bond at the α position of nitrogen.[209]

Shono developed a two-step oxidative coupling reaction of amides with nucleophiles.[213] For example, initial anodic oxidation of amide **5.20** gave iminium ion intermediate **5.21**, and subsequent nucleophilic addition of methanol provided the α-methoxy amide **5.22** (Scheme 5.2). The reaction was followed by addition of a nucleophile, such as silyl enol ether, vinyl ether, enamine or malonate, to **5.22** in the presence of a Lewis acid to afford α-substituted amide **5.23**. This strategy has been applied to the synthesis of pyrrolidine, piperidine and tropane alkaloids.[213]

Scheme 5.2

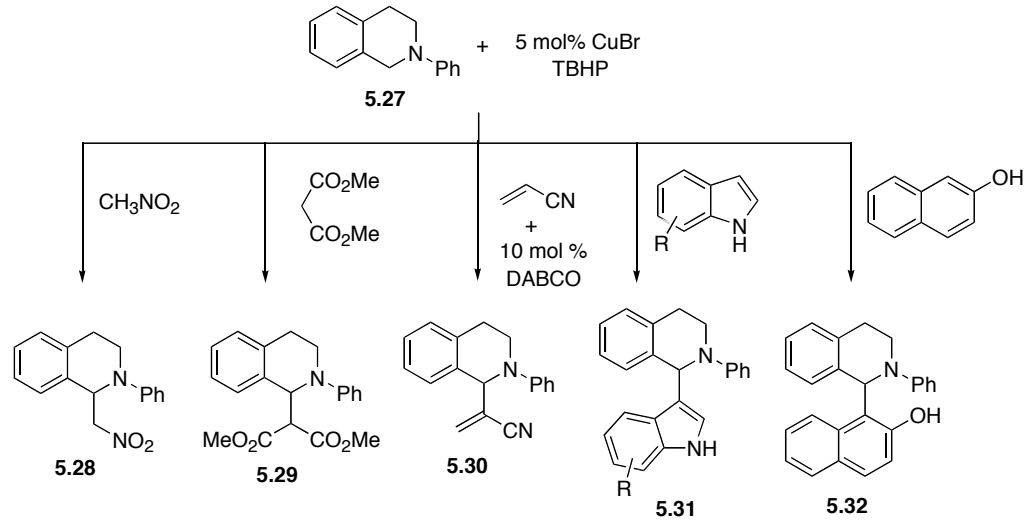


Transition metal-catalyzed C-H bond oxidations have also been used in oxidative Mannich reactions.[214] For example, Doyle reported a selective and efficient oxidative Mannich reaction catalyzed by $Rh_2(cap)_4$ in the presence of *tert*-butyl hydroperoxide (TBHP).[215] Inspired by a vinylogous Mannich reaction developed by our group,[216] the iminium ion derived from catalytic C-H oxidation of amine **5.24** was trapped by 2-siloxyfuran **5.25** to provide ϒ-aminoalkyl butenolide **5.26** (Eq 5.2). This reaction was extended to a diverse collection of amines and substituted 2-siloxyfurans. However, the role of $Rh_2(cap)_4$ in the catalytic generation of iminium ions was not clear.

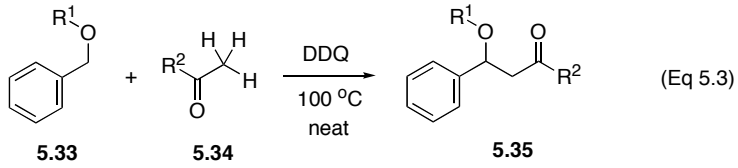


Li reported a mild cross-dehydrogenative-coupling reaction catalyzed by copper bromide in the presence of TBHP.[211,217] A new C–C bond was generated from the coupling of a tertiary amine with a nucleophile (Scheme 5.3). Nitroalkanes, malonates, vinyl cyanides, indoles, and 2-naphthols were found to be effective nucleophiles for these coupling reactions, and a variety of functionalized amines were thus prepared.

Scheme 5.3

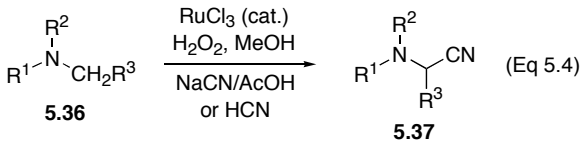


Li also reported a cross-dehydrogenative-coupling using DDQ as an oxidant (Eq 5.3).[218,219] This method allowed the direct coupling of benzyl ethers **5.33** and simple ketones **5.34** without using metal catalysts, but the reaction conditions were somewhat forcing.

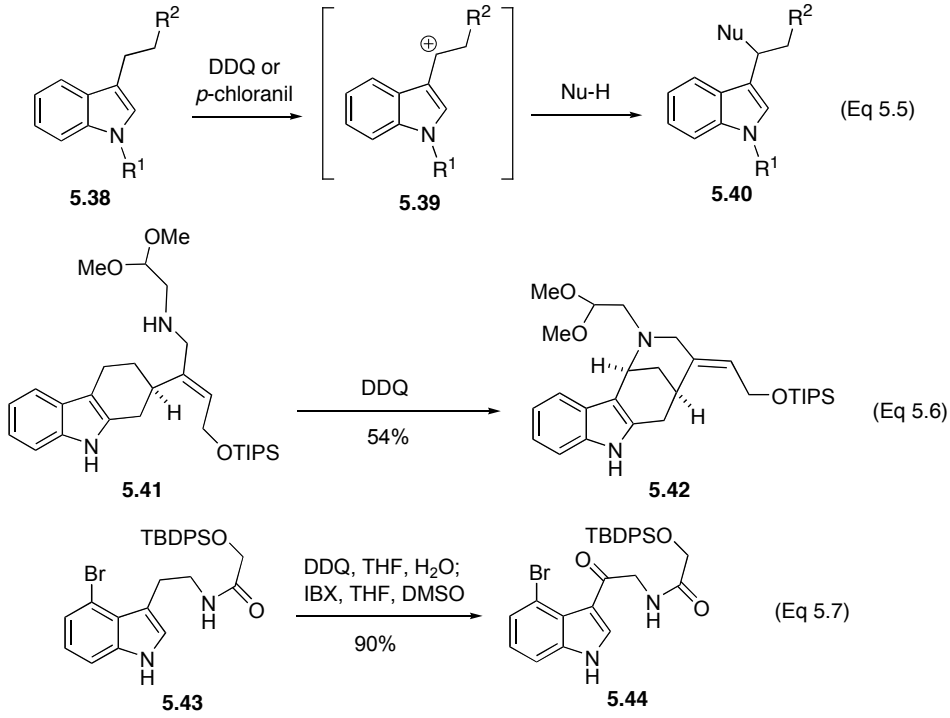


(Eq 5.3)

Murahashi demonstrated a highly efficient ruthenium-catalyzed oxidative cyanation of tertiary amines to provide the corresponding α-cyanated amines (Eq 5.4).[220] Isotope effect experiments suggested that cleavage of the C-H bond proceeds *via* an intermediate bearing more ionic character. The reaction presumably involved oxidation of tertiary amine **5.36** with ruthenium species to produce an iminium ion intermediate through electron and hydrogen transfer. Subsequent nucleophilic addition of hydrogen cyanide to the iminium ion generated the corresponding α-cyanated products **5.37**.



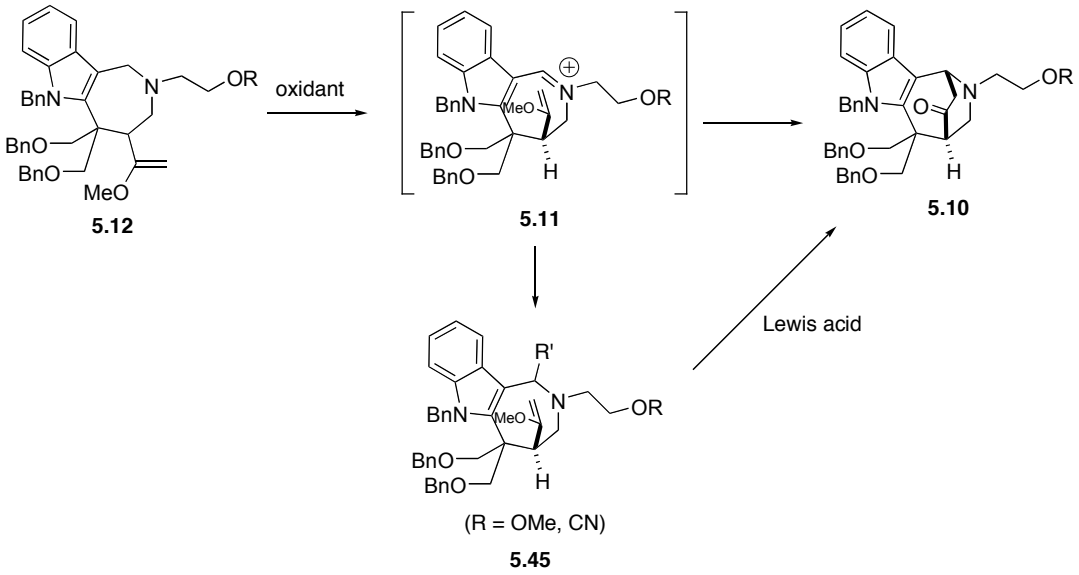
C3-Alkyl indoles, such as **5.38**, can be easily oxidized to a C3-carbocation intermediates **5.39** using DDQ or *p*-chloranil (Eq 5.5).[221,222,223] The resulting cations **5.39** can be trapped with various nucleophiles to give indoles **5.40**. Shibasaki reported that the oxidation of **5.41** with DDQ followed by intramolecular cyclization of a pendant nitrogen atom furnished indole **5.42** (Eq 5.6).[221] Nicolaou showed that oxidation of indole **5.43** with DDQ and subsequent addition of water provided an indolylalcohol, that was further oxidized with IBX to give the acyl indole **5.44** (Eq 5.7).[222]



Based upon the nature of C3-alkyl indole, which can be oxidized upon treatment with oxidant, we propose that the oxidation of indolyl amine **5.12** might generate the iminium ion intermediate **5.11** (Scheme 5.4). Beside DDQ and *p*-chloranil, suitable

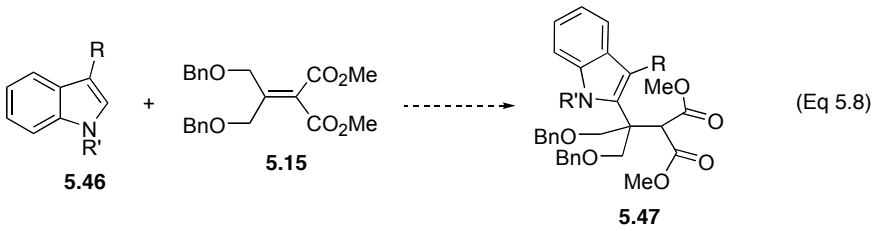
oxidants include $Rh_2(cap)_4$/TBHP, CuBr/TBHP and $RuCl_3/H_2O_2$, which have been employed in the oxidative Mannich reactions. Intermediate **5.11** is expected to be moderately stable due to electron delocalization by the nitrogen atom and the indole. Hydrolysis of the iminium ion is not expected to occur in the absence of nucleophiles like H_2O. Intramolecular nucleophlic addition of the enol ether to the iminium ion would afford **5.10**. Alternatively, if oxidation performs under Shono's or Murahashi's conditions (see Scheme 5.2 and Eq 5.4), addition of methanol or hydrogen cyanide to **5.11** may lead to **5.45**. Treatment of **5.45** with Lewis acid followed by addition of the pendent enol ether would provide **5.10**. Therefore, we hope that oxidative Mannich reaction will provide a potential route to the bicyclic product **5.10**.

Scheme 5.4



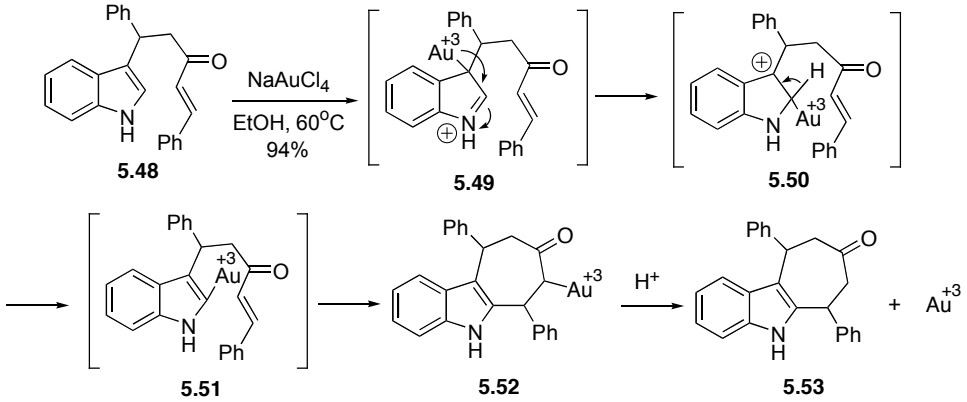
5.3 PROGRESS TOWARD THE SYNTHESIS OF ACTINOPHYLLIC ACID

We initially hoped to access malonates **5.47** utilizing metal-catalyzed 1,4-additions of indoles **5.46** with esters **5.15** (Eq 5.8). Arcadi reported that $NaAuCl_4 \cdot 2H_2O$ is an efficient catalyst for intramolecular conjugate addition of an indole to an α,β-unsaturated ketone moiety.[224] A plausible mechanism accounting for the gold-catalyzed reaction is depicted in Scheme 5.5. Regioselective auration of C3-substituted indole **5.48** occurs *via* electrophilic addition of the gold(III) to indole followed by rearrangement to form an intermediate **5.51**, which subsequently undergoes addition to α,β-enones to give σ-alkyl-gold species **5.52**. Protonolysis of **5.52** liberates the adduct **5.53** and regenerates the gold catalyst. $Pd(OAc)_2$, $PtCl_2$ and $Hf(OTf)_4$ have also been reported to catalyze arene metallation followed by 1,4-addition,[225,226,227] and may serve as effective catalysts for the synthesis of malonate **5.47**.



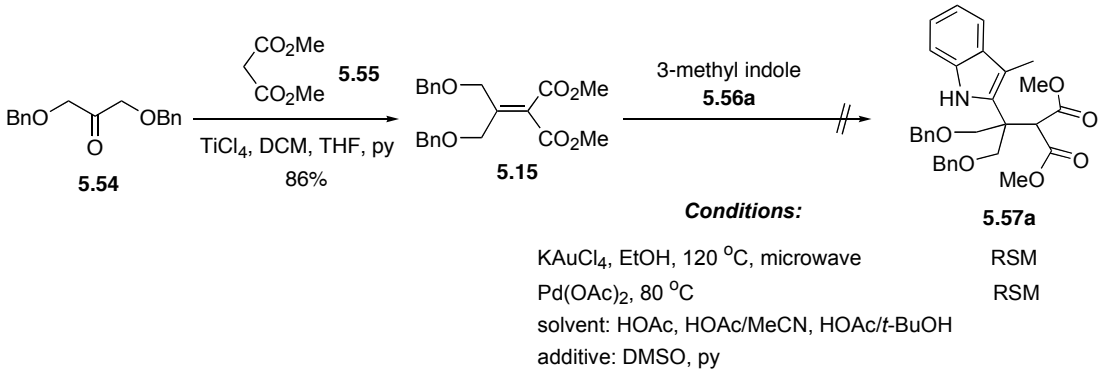
(Eq 5.8)

Scheme 5.5



In order to test the viability of the metal-catalyzed 1,4-conjugate addition for the synthesis of C2 malonate-substituted indole **5.57a**, we prepared bis(benzyloxyl)acetone (**5.54**) by oxidation of 1,3-bis(benzyloxyl)-2-propanol.[228] Then **5.54** was subjected to Knoevenagel condensation conditions in the presence of dimethyl manolate, titanium tetrachloride and pyridine to afford diester **5.15** in 86% yield (Scheme 5.6).[229] However, several attempts to perform the gold-catalyzed 1,4-addition of 3-methyl indole **5.56a** to **5.15** under the reported[224] or more forcing conditions only provided recovered starting materials. Changing the catalyst to $Pd(OAc)_2$ and screening various solvents and additives led to similar results.[226,227] These failures could be attributed to steric effects as the tetrasubstituted ester **5.15** is sterically hindered, and addition of a nucleophile to the β position of ester is presumably difficult.

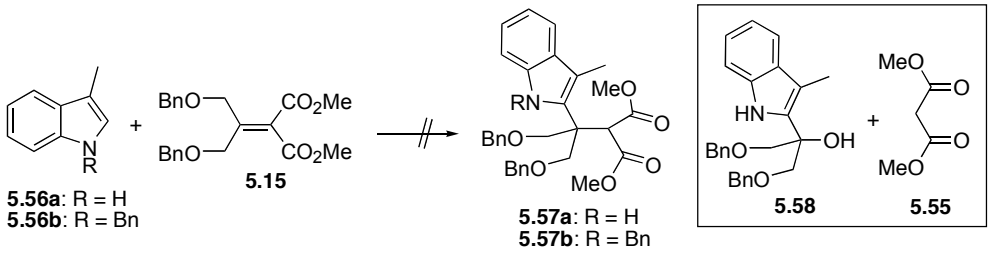
Scheme 5.6



Recently, Evans reported that the bis(oxazolinyl)pyridine-scandium(III) triflate complexes served as effective Lewis acid catalysts for the enantioselective Friedel-Crafts alkylation of α,β-unsaturated 2-acyl imidazoles with electron-rich arenes.[230] Tang demonstrated asymmetric Michael additions of indoles to alkylidene malonates by using oxazoline-copper(II) catalysts.[231] Moreover, zirconium(IV) chloride has been employed to catalyzed 1,4-additions of heterocyclic enamines, such as indoles, pyrroles, and

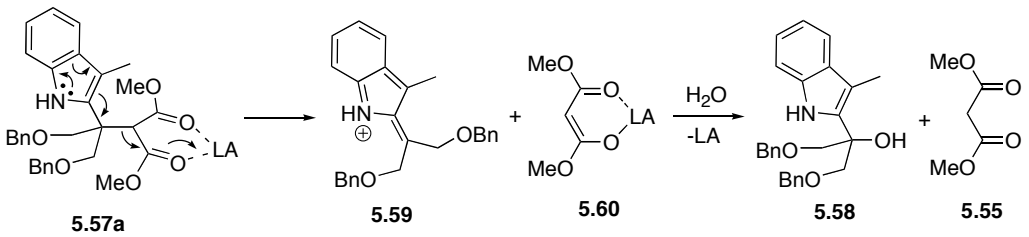
pyrazoles, to α,β-unsaturated olefins under mild conditions.[232] It is expected that these metal catalysts are capable of enhancing the electrophilicity of enones through chelation with carbonyl groups. Unfortunately, employing $Cu(OTf)_2$, $Sc(OTf)_3$ or $ZrCl_4$ complex to catalyze the 1,4-addition of 3-methyl indole **5.56a**-**b** to ester **5.15** afforded unreacted starting material or side product **5.58** and **5.55** (Scheme 5.7). The formation of **5.58** and **5.55** suggested that desired malonate **5.57a** had been generated, but it underwent retro-aldol type elimination to give **5.58** and **5.55** in the presence of Lewis acids (Scheme 5.8). Due to the problems encountered in the attempted conjugate addition, we decide to revise the synthesis of malonate **5.57**.

Scheme 5.7



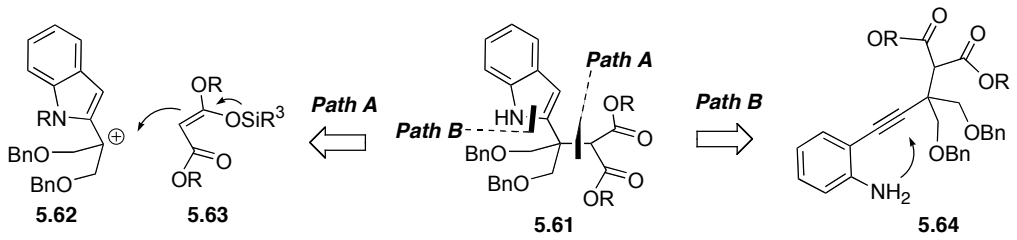
	Conditions:	***Results:***
5.56a	* $Cu(OTf)_2$, DCM or Ether	RSM
	* $Sc(OTf)_3$, THF (RT), Ether (RT), or MeCN (60 ^oC)	RSM
	* $Sc(OTf)_3$, DCM, 0 ^oC	**5.58** and **5.55**
	* $ZrCl_4$, DCM, RT	**5.58** and **5.55**
5.56b	* $Sc(OTf)_3$, DCM	RSM
	* $ZrCl_4$, DCM	RSM

Scheme 5.8



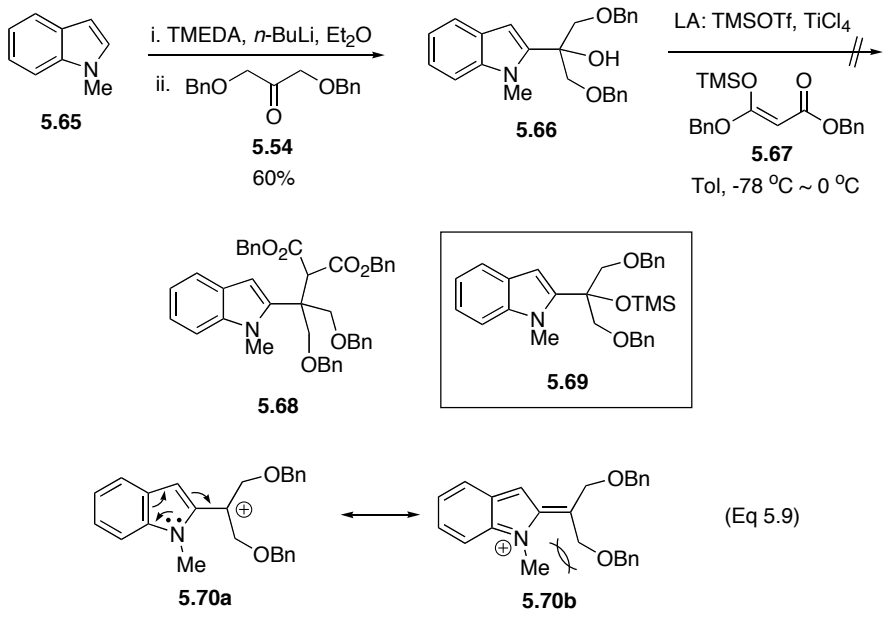
A substantial amount of work has been performed by Dr. Brian Gulledge, a former Martin Group postdoctoral associate, directed toward the vinylogous iminium S_N1-type coupling between a C3 indolyl alcohol and silyl ketene acetal using TMSOTf as Lewis acid catalyst.[233] Related research was reported by Rawal, who employed titanium chloride as catalyst.[234] From these advances, we expected that malonate **5.61** might arise from addition of an enol ether **5.63** to the tertiary carbocation **5.62** (Scheme 5.9, Path A). Another potential approach is the metal-catalyzed cyclization of 2-alkynylaniline **5.64** to provide indole **5.61** (Path B). Such cyclizations have been applied to the syntheses of a variety of indoles and have been reviewed in detail.[235]

Scheme 5.9



Based on the strategy of Path A, our efforts commenced with the synthesis of tertiary alcohol **5.66**. Selective deprotonation[236] of indole **5.65** with *n*-BuLi in the presence of TMEDA and subsequent addition to ketone **5.54** provided a tertiary alcohol **5.66** (Scheme 5.10). However, treatment of alcohol **5.66** with silyl enol ether **5.67**[237] in the presence of TMSOTf or $TiCl_4$ provided only small amounts of silyl ether **5.69** along with several unidentified compounds. Unfortunately, none of the desired product **5.68** was isolated. Presumbably, the generation of carbocation **5.70b** might be hard since steric repusion is presented in the conformation **5.70b** (Eq 5.9).

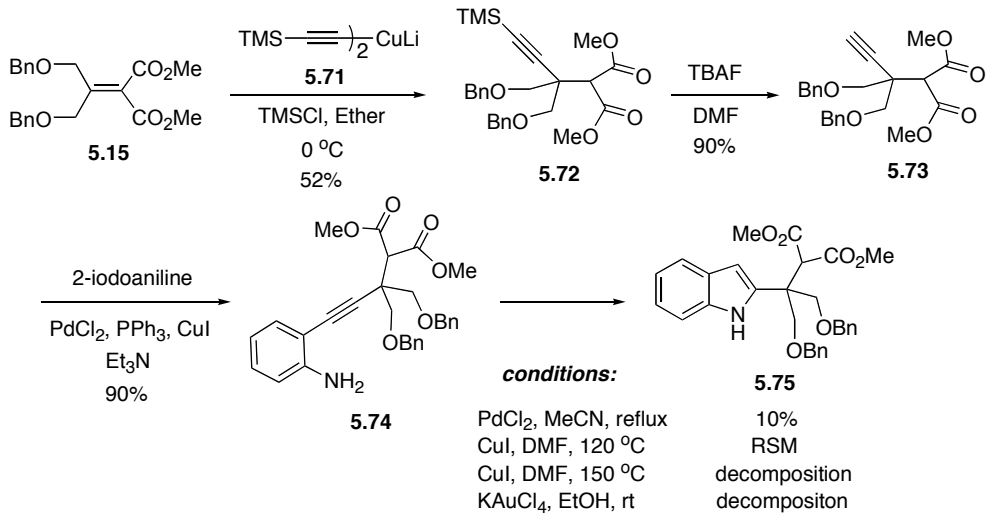
Scheme 5.10



At this point, we examined the feasibility of Path B. The conjugate addition of diethynylcuprate **5.71** to ester **5.15** initially provided an internal alkyne **5.72** in less than 35% yield (Scheme 5.11). A variety of Lewis acid additives were examined to improve the yield, including TMSCl, $BF_3{\cdot}Et_2O$, $TiCl_4$, $AlCl_3$, and TMSOTf. The best result was obtained with the addition of TMSCl[238] providing alkyne **5.72** in 52% yield. The TMS group was removed upon treatment with TBAF to give a terminal alkyne **5.73**, which underwent Sonogashira cross-coupling[239] with *o*-iodoaniline to give **5.74** in 81% yield over two steps. However, the attempted metal-catalyzed cyclization of 2-alkynylaniline **5.74** to the corresponding indole **5.75** did not provide promising results. When $PdCl_2$ was employed as catalyst[240], indole **5.75** was generated in only 10% yield together with a mixture of unidentified baseline materials. Attempts to effect cyclization using CuI[239] or $KAuCl_4$ [241] led to recovered starting material or decomposition. In subsequent investigations, we found that indole **5.75** was not stable toward $PdCl_2$, CuI, or $KAuCl_4$

catalyst. The retro-aldol type elimination (see Scheme 5.8) was presumably a potential side reaction since malonate at the α position of the C2 indole was a good leaving group. If this side reaction occurred, dimethyl malonate should fall apart from the indole. However, the crude ^{1}H NMR spectra of these crude reactions were inconclusive regarding the presence of dimethyl malonate. At this point, we decided to synthesize **5.76** by removing one of the ester in 2-alkynylaniline **5.74** prior to examining the cyclization.

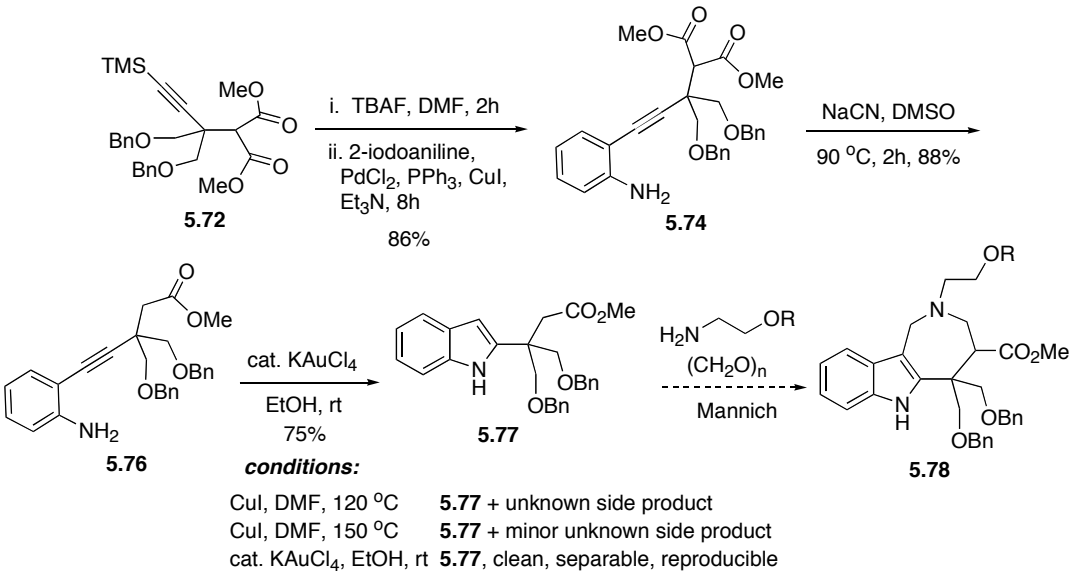
Scheme 5.11



The conversion of internal alkyne **5.72** to 2-alkynylaniline **5.74** originally required two steps, but a one-step procedure for this conversion was devised. Namely, the TMS group was first cleaved with TBAF to give an alkyne **5.73** intermediate, which was transformed to **5.74** in 86% yield in the same pot reaction upon addition of palladium and copper catalysts to the reaction mixture (Scheme 5.12). Krapcho dealkoxycarbonylation of aniline **5.74** with NaCN[242] in DMSO furnished monoester **5.76** in 88% yield. Cyclization of **5.76** using copper iodide provided the desired indole **5.77** together with a small amount of an inseparable, unknown side product. When $KAuCl_4$ was employed as

catalyst, cyclization gave indole **5.77** in 75% yield. This successful annulation could be attributed to the stability of monoester **5.77** toward the catalytic conditions. Future work will involve exploring the tandem Mannich reaction for the synthesis of azepino[4,3-*b*]indole **5.78** and then examining the possibility of the key oxidative Mannich reaction.

Scheme 5.12



5.4 SUMMARY

Although the oxidative Mannich reaction has received much attention recently, it has not been applied to the synthesis of indole alkaloids and any natural products. We propose an oxidative Mannich reaction for the synthesis of an indole natural product, actinophyllic acid. The synthesis features the selective oxidation of a C3-alkyl indole followed by intramolecular nucleophilic addition of an enol ether to build a bicylcic framework.

Our project toward the synthesis of actinophyllic acid has been initiated.

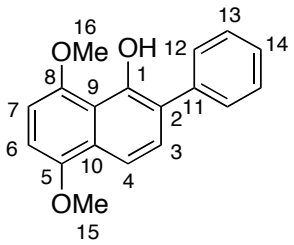
Currently, we have prepared indole **5.77**. Continuing efforts will be focused on the formation of azepino[4,3-*b*]indole **5.78** and the key oxidative Mannich reaction. We hope that an oxidative Mannich strategy will provide a convergent access to the skeleton of actinophyllic acid.

Chapter 6. Experimental Procedures

6.1 General

Tetrahydrofuran, dimethylformamide, acetonitrile, and toluene were dried according to the procedure described by Grubbs.[243] All solvents were determined to contain less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. Triethylamine was distilled from calcium hydride prior to use. Zn powder was activated by washing with 2% aqueous HCl and dried in vacuo at room temperature prior to use.[244] Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Thin layer chromatography was run on pre-coated silica gel plates with a 0.25 mm thickness containing 60F-254 indicator (Merck), and the plates were visualized by staining with AMCAN (ammonium molybdate/cerium ammonium nitrate), potassium permagnate, or *p*-anisaldehyde. Flash chromatography was performed using the indicated solvent system on 230-400 mesh silica gel (E. Merck reagent silica gel 60) according to Still's protocol.[245] Melting points are uncorrected. Infrared (IR) spectra were obtained as solutions in the solvent indicated. Proton nuclear magnetic resonance spectra (^{1}H NMR) were obtained as solutions in the indicated deuterated solvent, and chemical shifts are reported in parts per million (ppm) referenced to the solvent. Coupling constants (*J*) are reported in Hz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; app t, apparent triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained using the solvent indicated as the internal reference.

6.2 COMPOUND

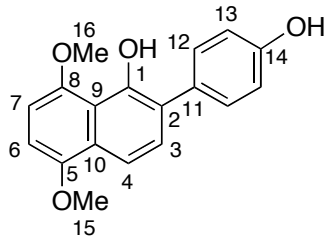


2.18

5,8-Dimethoxy-2-phenyl-1-naphthol (2.18) [Notebook CLC1-38]. A mixture of $Pd(Ph_3P)_4$ (11.4 mg, 0.01 mmol), K_2CO_3 (15 mg, 0.11 mmol) and cycloadduct **2.7a** (20 mg, 0.10 mmol) in 5 mL round bottom flask was purged with argon for three times. The phenyl iodide (12 μl, 0.11 mmol) and DMF (2 mL) were added successively, and the solution was bubbled with argon for 10 min. The reaction was stirred for 15 h at 110 °C. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuum. The crude product was purified by flash chromatography, eluting with 5% EtOAc in hexanes to give 16 mg (58%) of **2.18** as a white solid; ^{1}H NMR (250 MHz) δ 9.97 (s, 1 H), 7.80 (d, *J* = 8.6 Hz, 1 H), 7.71 (d, *J* = 8.5 Hz, 2 H), 7.49 (d, *J* = 8.9 Hz, 2 H), 7.42 (s, 1 H), 7.36 (d, *J* = 7.2 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1 H), 6.66 (d, *J* = 8.5 Hz, 1 H), 3.99 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (75 MHz) δ 150.8, 150.3, 150.2, 138.8, 129.7, 129.2, 128.0, 127.4, 126.6, 123.8, 115.8, 113.0, 104.1, 103.1, 56.5, 55.7; IR ($CDCl_3$) 3359, 2942, 1614, 1615, 1456, 1392, 1251 cm^{-1}; mass spectrum (CI) *m/z* 281.1175 [$C_{18}H_{17}O_3$ (M+1) requires 281.1178] (base), 265.

NMR Assignments. ^{1}H NMR (250 MHz) δ 9.97 (s, 1 H, OH), 7.80 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.71 (d, *J* = 8.5 Hz, 2 H, C12-H), 7.49 (d, *J* = 8.9 Hz, 2 H, C13-H), 7.42 (s, 1 H, C14-H), 7.36 (d, *J* = 7.2 Hz, 1 H, C4-H), 6.71 (d, *J* = 8.5 Hz, 1 H, C7-H), 6.66 (d, *J* = 8.5 Hz, 1 H, C6-H), 3.99 (s, 3 H, C16-H), 3.95 (s, 3 H, C15-H); ^{13}C NMR (75 MHz) δ

150.8 (C1), 150.3 (C8), 150.2 (C5), 138.8, 129.7, 129.2, 128.0, 127.4, 126.6, 123.8, 115.8, 113.0, 104.1, 103.1, 56.5 (OCH_3), 55.7 (OCH_3).



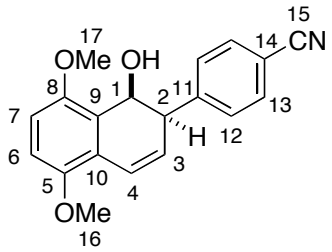
2.19

2-(4-Hydroxy-phenyl)-5,8-dimethoxy-1-naphthol (2.19) [Notebook CLC1-31]. A mixture of $Pd(Ph_3P)_4$ (11.4 mg, 0.0098 mmol), K_2CO_3 (15 mg, 0.11 mmol), *p*-iodophenol (25.2 mg, 0.10 mmol) and cycloadduct **2.7a** (20 mg, 0.098 mmol) in 5 mL round bottom flask was purged with argon for three times. DMF (2 mL) were added, and the solution was bubbled with argon for 10 mins. The reaction was stirred for 15 h at 110 °C. The mixture was filtered through a pad of Celite, and the filtrate was concentrated in vacuum. The crude product was purified by flash chromatography, eluting with 5% EtOAc in hexanes to give 12 mg (41%) of **2.19** as a white solid; ^{1}H NMR (250 MHz) δ 8.38 (s, 1 H), 8.26 (d, *J* = 8.4 Hz, 1 H), 7.74 (d, *J* = 8.4 Hz, 1 H), 7.64 (d, *J* = 8.8 Hz, 2 H), 6.94 (d, *J* = 8.4 Hz, 2 H), 6.72 (d, *J* = 8.0 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 5.75 (br, 1 H), 3.96 (s, 6 H); ^{13}C NMR (75 MHz) δ 155.3, 149.6, 149.4, 138.0, 133.8, 128.6, 126.6, 125.1, 125.0, 122.3, 119.0, 115.7, 103.7, 103.1, 55.7; IR ($CDCl_3$) 3359, 2973, 2251, 1611, 1519, 1392, 1250 cm^{-1}; mass spectrum (CI) *m/z* 295.1332 [$C_{18}H_{15}O_4$ requires (M-1) 295.1334].

NMR Assignments. ^{1}H NMR (250 MHz) δ 8.38 (s, 1 H, OH), 8.26 (d, *J* = 8.4 Hz, 1 H, C3-H), 7.74 (d, *J* = 8.4 Hz, 1 H, C4-H), 7.64 (d, *J* = 8.8 Hz, 2 H, C12-H), 6.94 (d, *J* = 8.4 Hz, 2 H, C13-H), 6.72 (d, *J* = 8.0 Hz, 1 H, C7-H), 6.68 (d, *J* = 8.4 Hz, 1 H,

C6-H), 5.75 (br, 1 H, OH), 3.96 (s, 6 H, OCH_3); ^{13}C NMR (75 MHz) δ 155.3 (C1), 149.6 (C8), 149.4 (C5), 138.0, 133.8, 128.6, 126.6, 125.1, 125.0, 122.3, 119.0, 115.7, 103.7, 103.1, 55.7 (C15 & C16).

General procedure for palladium-catalyzed ring opening of bicyclic alkenes. 1,2,2,6,6-Pentamethylpiperidine (PMP) (67 μL, 0.37 mmol) was added to a mixture of bicyclic alkene (0.74 mmol), aryl or vinyl halide (0.88 mmol), $Pd(OAc)_2$ (9 mg, 5 mol %), PPh_3 (21 mg, 11 mol %) and activated Zn (480 mg, 7.4 mmol) in DMF (14.7 mL) under argon. The resulting mixture was heated at the indicated bath temperature (see Tables 2.4 and 2.5) with stirring until the starting bicyclic alkene was fully consumed as indicated by TLC. The reaction was allowed to cool to room temperature, 50% EtOAc/hexanes (60 mL) were added, and the mixture was filtered through a pad of celite. The filtrate was washed with brine (4 x 10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with EtOAc/hexanes in the ratio given to provide the 2-substituted-1,2-dihydro-1-naphthol derivatives (**2.32a**-**2.44a**, **2.45**-**2.49**).

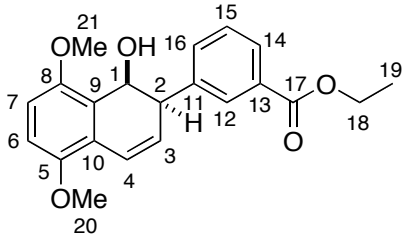


2.33a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(4-cyanophenyl)-1-naphthol (2.33a) [Notebook CLC2-194].** 50% EtOAc/hexanes; light yellowish solid; mp: 175-176 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 7.69-7.61 (m, 2 H), 7.55-7.48 (m, 2 H), 7.10 (dd, J = 9.8, 3.1

Hz, 1 H), 6.84 (d, *J* = 9.0 Hz, 1 H), 6.80 (d, *J* = 9.0 Hz, 1 H), 6.03 (ddd, *J* = 9.8, 2.3, 1.5 Hz, 1 H), 5.08 (ddd, *J* = 6.2, 4.7, 1.5 Hz, 1 H), 3.86-3.77 (comp, 7 H), 1.63 (d, *J* = 6.2 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.4, 149.7, 146.5, 132.0, 130.0, 127.2, 124.0, 122.6, 121.9, 119.0, 111.5, 111.1, 110.6, 64.2, 56.1, 56.0, 47.3; IR ($CDCl_3$) 3606, 2928, 2228, 1604, 1485, 1263, 1088 cm^{-1}; mass spectrum (CI) *m/z* 308.1289 [$C_{19}H_{18}NO_3$ (M+1) requires 308.1287], 290 (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.69-7.61 (m, 2 H, C13-H), 7.55-7.48 (m, 2 H, C12-H), 7.10 (dd, *J* = 9.8, 3.1 Hz, 1 H, C4-H), 6.84 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.80 (d, *J* = 9.0 Hz, 1 H, C7-H), 6.03 (ddd, *J* = 9.8, 2.3, 1.5 Hz, 1 H, C3-H), 5.08 (ddd, *J* = 6.2, 4.7, 1.5 Hz, 1 H, C1-H), 3.86-3.77 (comp, 7H, C2-H, C17-H & C16-H), 1.63 (d, *J* = 6.2 Hz, 1 H, OH); ^{13}C NMR (62.5 MHz) δ 150.4, 149.7, 146.5, 132.0, 130.0, 127.2, 124.0, 122.6, 121.9, 119.0, 111.5, 111.1, 110.6 (Csp^2 & C15), 64.2 (C1), 56.1 (C17), 56.0 (C16), 47.3 (C2).



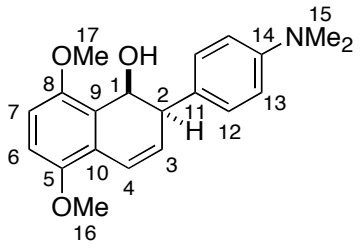
2.34a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(3-ethoxycarbonylphenyl)-1-naphthol**

(2.34a) [Notebook CLC2-191]. 50% EtOAc/hexanes; light yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.08 (s, 1 H), 7.98 (d, *J* = 7.7 Hz, 1 H), 7.62 (d, *J* = 7.7 Hz, 1 H), 7.45 (t, *J* = 7.7 Hz, 1 H), 7.10 (dd, *J* = 9.9, 3.2 Hz, 1 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 6.78 (d, *J* = 9.0 Hz, 1 H), 6.16-6.08 (m, 1 H), 5.09 (ddd, *J* = 6.0, 4.7, 1.3 Hz, 1 H), 4.37 (q, *J* = 7.1 Hz, 2 H), 3.89-3.76 (m, 7 H), 1.55 (d, *J* = 6.0 Hz, 1 H), 1.38 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR

(62.5 MHz, $CDCl_3$) δ 166.6, 150.5, 149.6, 141.0, 133.6, 130.5, 130.1, 128.3, 128.2, 128.1, 124.3, 122.3, 122.2, 111.4, 111.0, 64.1, 60.9, 56.1, 56.0, 47.0, 14.3; IR ($CDCl_3$) 3595, 2939, 1712, 1598, 1485, 1257, 1088 cm^{-1}; mass spectrum (CI) *m/z* 354.1483 [$C_{21}H_{22}O_5$ requires 354.1467], 337 (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 8.08 (s, 1 H, C12-H), 7.98 (d, *J* = 7.7 Hz, 1 H, C14-H), 7.62 (d, *J* = 7.7 Hz, 1 H, C16-H), 7.45 (t, *J* = 7.7 Hz, 1 H, C15-H), 7.10 (dd, *J* = 9.9, 3.1 Hz, 1 H, C4-H), 6.83 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.78 (d, *J* = 9.0 Hz, 1 H, C7-H), 6.16-6.08 (m, 1 H, C3-H), 5.09 (ddd, *J* = 6.0, 4.7, 1.3 Hz, 1 H, C1-H), 4.37 (q, *J* = 7.1 Hz, 2 H, C18-H), 3.89-3.76 (m, 7 H, C2-H, C21-H & C20-H), 1.55 (d, *J* = 6.0 Hz, 1 H, OH), 1.38 (t, *J* = 7.1 Hz, 3 H, C19-H); ^{13}C NMR (62.5 MHz) δ 166.6 (C17), 150.5, 149.6, 141.0, 133.6, 130.5, 130.1, 128.3, 128.2, 128.1, 124.3, 122.3, 122.2, 111.4, 111.0 (Csp^2), 64.1 (C1), 60.9 (C18), 56.1 (C21), 56.0 (C20), 47.0 (C2), 14.3 (C19).

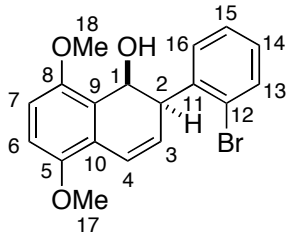


2.36a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(4-N,N-dimethylanilinyl)-1-naphthol (2.36a) [Notebook CLC2-216].** 50% EtOAc/hexanes; white solid; mp: 122-123 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.34-7.24 (m, 2 H), 7.04 (dd, *J* = 9.8, 3.1 Hz, 1 H), 6.83-6.72 (comp, 4 H), 6.11 (ddd, *J* = 9.8, 2.4, 1.5 Hz, 1 H), 5.04-4.98 (m, 1 H), 3.81 (s, 3 H), 3.80 (s, 3 H), 3.75-3.67 (m, 1 H), 2.94 (s, 6 H), 1.56 (d, *J* = 4.6 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.8, 149.8, 149.6, 129.7, 129.6, 127.7, 124.3, 122.6, 121.7, 113.0, 111.3, 110.8, 64.3, 56.1, 56.0, 46.2, 40.7; IR ($CDCl_3$) 3599, 2938, 1613, 1483, 1259,

1089 cm^{-1}; mass spectrum (CI) *m/z* 325.1671 [$C_{20}H_{23}NO_3$ requires 325.1678], 308 (base), 205.

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.32-7.24 (m, 2 H, C12-H), 7.04 (dd, *J* = 9.8, 3.1 Hz, 1 H, C4-H), 6.83-6.72 (comp, 4 H, C13-H, C6-H & C7-H), 6.11 (ddd, *J* = 9.8, 2.4, 1.5 Hz, 1 H, C3-H), 5.04-4.98 (m, 1 H, C1-H), 3.81 (s, 3 H, C17-H), 3.80 (s, 3 H, C16-H), 3.75-3.67 (m, 1 H, C2-H), 2.94 (s, 6 H, C15-H), 1.56 (d, *J* = 4.6 Hz, 1 H, OH); ^{13}C NMR (62.5 MHz) δ 150.8, 149.8, 149.6, 129.7, 129.6, 127.7, 124.3, 122.6, 121.7, 113.0, 111.3, 110.8 (Csp^2), 64.3 (C1), 56.1 (C17), 56.0 (C16), 46.2 (C2), 40.7 (C15).



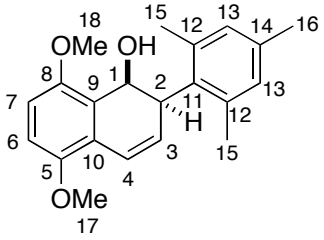
2.37a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(2-bromophenyl)-1-naphthol (2.37a)**

[Notebook CLC2-187]. 15% EtOAc/hexanes; yellowish solid; mp: 93-94 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.63-7.45 (comp, 2 H), 7.33 (dt, *J* = 7.5, 1.3 Hz, 1 H), 7.19-7.06 (comp, 2 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 6.79 (d, *J* = 9.0 Hz, 1 H), 6.08-5.99 (m, 1 H), 5.26-5.19 (m, 1 H), 4.34-4.27 (m, 1 H), 3.82 (s, 6 H), 1.46 (d, *J* = 5.9 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.7, 149.5, 139.4, 132.5, 131.5, 128.6, 128.4, 127.3, 124.6, 124.0, 122.0, 121.9, 111.3, 111.0, 61.4, 56.1, 56.0, 46.4; IR ($CDCl_3$) 3590, 2939, 1597, 1483, 1261, 1089 cm^{-1}; mass spectrum (CI) *m/z* 360.0359 [$C_{18}H_{17}O_3Br$ requires 360.0361], 343 (base), 281, 264.

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.63-7.45 (comp, 2 H, C13-H & C-16-H), 7.33 (dt, *J* = 7.5, 1.3 Hz, 1 H, C15-H), 7.19-7.06 (comp, 2 H, C14-H & C4-H),

6.83 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.79 (d, *J* = 9.0 Hz, 1 H, C7-H), 6.08-5.99 (m, 1 H, C3-H), 5.26-5.19 (m, 1 H, C1-H), 4.34-4.27 (m, 1 H, C2-H), 3.82 (s, 6 H, C18-H & C17-H), 1.46 (d, *J* = 5.9 Hz, 1 H, OH); ^{13}C NMR (62.5 MHz) δ 150.7, 149.5, 139.4, 132.5, 131.5, 128.6, 128.4, 127.3, 124.6, 124.0, 122.0, 121.9, 111.3, 111.0 (Csp^2), 61.4 (C1), 56.1 (C18), 56.0 (C17), 46.4 (C2).

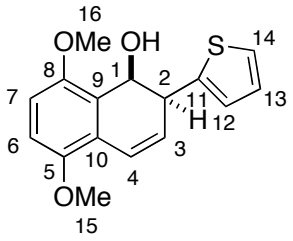


2.38a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-mesityl-1-naphthol (2.38a) [Notebook CLC3-23].** 15% EtOAc/hexanes; white solid; mp 117-118 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.95 (dd, *J* = 9.8, 3.4 Hz, 1 H), 6.89 (s, 2 H), 6.82 (d, *J* = 8.9 Hz, 2 H), 6.76 (d, *J* = 8.9 Hz, 1 H), 6.21 (ddd, *J* = 9.8, 3.4, 1.2 Hz, 1 H), 5.16 (ddd, *J* = 5.5, 4.2, 1.2 Hz, 2 H), 4.13-4.02 (m, 1 H), 3.82 (s, 3 H), 3.80 (s, 3 H), 2.48 (s, 3 H), 2.34 (s, 3 H), 2.26 (s, 3 H), 1.65 (d, *J* = 4.2 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.9, 149.4, 139.2, 136.7, 135.9, 133.2, 131.9, 130.7, 129.0, 124.4, 122.7, 117.5, 111.1, 109.9, 62.7, 56.1, 55.9, 42.3, 21.4, 20.9, 20.6; IR ($CDCl_3$) 3597, 2939, 1598, 1482, 1262, 1086 cm^{-1}; mass spectrum (CI) *m/z* 325.1802 [$C_{21}H_{25}O_3$ (M+1) requires 325.1804], 307 (base), 205.

NMR Assignments. ^{1}H NMR (400 MHz) δ 6.95 (dd, *J* = 9.8, 3.4 Hz, 1 H, C4-H), 6.89 (s, 2 H, C13-H), 6.82 (d, *J* = 8.9 Hz, 2 H, C6-H), 6.76 (d, *J* = 8.9 Hz, 1 H, C7-H), 6.21 (ddd, *J* = 9.8, 3.4, 1.2 Hz, 1 H, C3-H), 5.16 (d, *J* = 5.5, 4.2, 1.2 Hz, 2 H, C1-H), 4.13 -4.02 (m, 1 H, C2-H), 3.82 (s, 3 H, C17 or C18-H), 3.80 (s, 3 H, C17 or C18-H), 2.48 (s, 3 H, C16-H), 2.34 (s, 3 H, C15-H), 2.26 (s, 3 H, C15-H), 1.65 (d, *J* = 4.2 Hz, 1 H, OH);

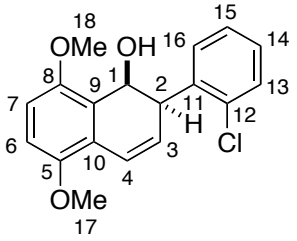
^{13}C NMR (75 MHz) δ 150.9, 149.4, 139.2, 136.7, 135.9, 133.2, 131.9, 130.7, 129.0, 124.4, 122.7, 117.5, 111.1, 109.9 (sp^2-C), 62.7 (C1), 56.1 (C18), 55.9 (C17), 42.3 (C2), 21.4 (C16), 20.9 (C15), 20.6 (C15).



2.39a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(2-thienyl)-1-naphthol (2.39a) [Notebook CLC3-58].** 25% EtOAc/hexanes; orange oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27-7.24 (m, 1 H), 7.12-7.09 (m, 1 H), 7.07-7.00 (comp, 2 H), 6.82 (d, *J* = 9.1 Hz, 1 H), 6.78 (d, *J* = 9.1 Hz, 1 H), 6.07 (ddd, *J* = 9.8, 2.4, 1.4 Hz, 1 H), 5.17-5.10 (m, 1 H), 4.12-4.05 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H), 1.83 (d, *J* = 5.4 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.7, 149.6, 143.1, 128.5, 126.8, 125.6, 124.3, 124.2, 122.2, 122.0, 111.5, 111.1, 64.5, 56.1, 56.0, 42.7; IR ($CDCl_3$) 3594, 2938, 1602, 1486, 1259, 1087 cm^{-1}; mass spectrum (CI) *m/z* 288.0831 [$C_{16}H_{16}O_3S$ requires 288.0820], 271 (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.27-7.24 (m, 1 H, C14-H), 7.12-7.09 (m, 1 H, C12-H), 7.07-7.00 (comp, 2 H, C4-H & C13-H), 6.82 (d, *J* = 9.1 Hz, 1 H, C6-H), 6.78 (d, *J* = 9.1 Hz, 1 H, C7-H), 6.07 (ddd, *J* = 9.8, 2.4, 1.4 Hz, 1 H, C3-H), 5.17-5.10 (m, 1 H, C1-H), 4.12-4.05 (m, 1 H, C2-H), 3.82 (s, 3 H, C16-H), 3.81 (s, 3 H, C15-H), 1.83 (d, *J* = 5.4 Hz, 1 H, OH); ^{13}C NMR (62.5 MHz) δ 150.7, 149.6, 143.1, 128.5, 126.8, 125.6, 124.3, 124.2, 122.2, 122.0, 111.5, 111.1, 64.5 (C1), 56.1 (C16), 56.0 (C15), 42.7 (C2).

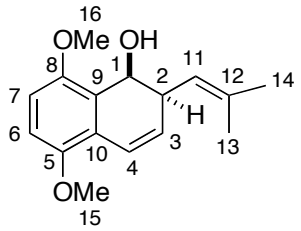


2.40a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(2-chlorophenyl)-1-naphthol (2.40a)**

[Notebook CLC2-154]. 50% EtOAc/hexanes; yellowish solid; mp: 98-99 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.52-7.18 (comp, 4 H), 7.10 (dd, *J* = 9.9, 3.1 Hz, 1 H), 6.83 (d, *J* = 9.0 Hz, 1 H), 6.79 (d, *J* = 9.0 Hz, 1 H), 6.08-6.00 (m, 1 H), 5.21 (ddd, *J* = 5.9, 4.7, 1.5 Hz, 1 H), 4.37-4.29 (m, 1 H), 3.82 (s, 3 H), 3.81 (s, 3 H,), 1.46 (d, *J* = 5.9 Hz, 1 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.7, 149.5, 137.9, 133.9, 131.4, 129.3, 128.5, 128.1, 126.7, 124.1, 122.1, 122.0, 111.4, 111.0, 61.5, 56.1, 56.0, 43.8; IR ($CDCl_3$) 3593, 2939, 1596, 1483, 1261, 1089 cm^{-1}; mass spectrum (CI) *m/z* 316.0864 [$C_{18}H_{17}O_3Cl$ requires 316.0866], 299 (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.52-7.18 (comp, 4 H, C13-H, C14-H, C15-H & C16-H), 7.10 (dd, *J* = 9.9, 3.1 Hz, 1 H, C4-H), 6.83 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.79 (d, *J* = 9.0 Hz, 1H, C7-H), 6.08-6.00 (m, 1 H, C3-H), 5.21 (ddd, *J* = 5.9, 4.7, 1.5 Hz, 1H, C1-H), 4.37-4.29 (m, 1 H, C2-H), 3.82 (s, 3 H, C18-H), 3.81 (s, 3 H, C17-H), 1.46 (d, 1 H, *J* = 5.9 Hz, OH); ^{13}C NMR (62.5 MHz) δ 150.7, 149.5, 137.9, 133.9, 131.4, 129.3, 128.5, 128.1, 126.7, 124.1, 122.1, 122.0, 111.4, 111.0 (Csp^2), 61.5 (C1), 56.1 (C18), 56.0 (C17), 43.8 (C2).

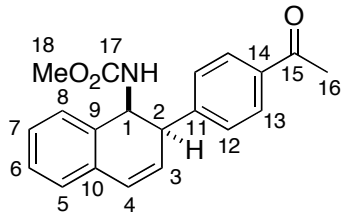


2.41a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(2-methyl-propenyl)-1-naphthol (2.41a)**

[Notebook CLC3-63]. 20% EtOAc/hexanes; orange oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 9.8, 3.1 Hz, 1 H), 6.79 (d, *J* = 9.0 Hz, 1 H), 6.74 (d, *J* = 9.0 Hz, 1 H), 5.80-5.71 (m, 1 H), 5.62-5.53 (m, 1 H), 4.93 (ddd, *J* = 6.4, 4.7, 1.2 Hz, 1 H), 3.81 (s, 3 H), 3.79 (s, 3 H), 3.34-3.24 (m, 1 H), 1.80 (d, *J* = 1.1 Hz, 3 H), 1.77 (d, *J* = 6.4 Hz, 1 H), 1.69 (d, *J* = 1.3 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.5, 149.5, 134.4, 130.6, 125.2, 122.4, 122.3, 120.8, 111.1, 110.6, 63.6, 56.1, 56.0, 39.6, 25.9, 18.2; IR ($CDCl_3$) 3586, 2937, 1597, 1483, 1259, 1088 cm^{-1}; mass spectrum (CI) *m/z* 260.1400 [$C_{16}H_{20}O_3$ requires 260.1412], 243 (base).

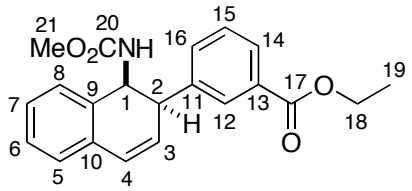
NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.91 (dd, *J* = 9.8, 3.1 Hz, 1 H, C4-H), 6.79 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.74 (d, *J* = 9.0 Hz, 1 H, C7-H), 5.80-5.71 (m, 1 H, C3-H), 5.62-5.53 (m, 1 H, C11-H), 4.93 (ddd, *J* = 6.4, 4.7, 1.2 Hz, 1 H, C1-H), 3.81 (s, 3 H, C16-H), 3.79 (s, 3 H, C15-H), 3.34-3.24 (m, 1 H, C2-H), 1.80 (d, *J* = 1.1 Hz, 3 H, C14-H), 1.77 (d, *J* = 6.4 Hz, 1 H, OH), 1.69 (d, *J* = 1.3 Hz, 3 H, C14-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.5 (C8), 149.5 (C5), 134.4, 130.6, 125.2, 122.4, 122.3, 120.8, 111.1, 110.6, 63.6 (C1), 56.1 (C16), 56.0 (C15), 39.6 (C2), 25.9 (C14), 18.2 (C13).



2.45

Methyl *N*-[*cis*-1,2-dihydro-2-(4-acetylphenyl)-1-naphthyl]carbamate (2.45) [Notebook CLC3-36]. 30% EtOAc/hexanes; yellow solid; mp 112-113 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85-7.77 (m, 2 H), 7.32-7.13 (comp, 6 H), 6.71 (dd, *J* = 9.6, 1.5 Hz, 1 H), 6.11 (d, *J* = 9.6, 4.8 Hz, 1 H), 5.35 (dd, *J* = 10.3, 7.0 Hz, 1 H), 4.66 (d, *J* = 10.3 Hz, 1 H), 3.96-3.85 (m, 1 H), 3.60 (s, 3 H), 2.54 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.4, 156.3, 143.1, 136.0, 134.4, 134.0, 132.7, 129.0, 128.8, 128.3, 128.2, 127.9, 126.4, 125.4, 52.6, 52.1, 44.6, 26.3; IR ($CDCl_3$) 3320, 2952, 1721, 1681, 1519, 1269 cm^{-1}; mass spectrum (CI) *m/z* 322.1445 [$C_{20}H_{20}NO_3$ (M+1) requires 322.1443] (base), 247.

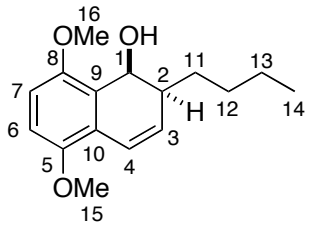
NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.85-7.77 (m, 2 H, C13-H), 7.32-7.13 (comp, 6 H, C5-H, C6-H, C7-H, C8-H & C12-H), 6.71 (dd, *J* = 9.6, 1.5 Hz, 1 H, C4-H), 6.11 (d, *J* = 9.6, 4.8 Hz, 1 H, C3-H), 5.35 (dd, *J* = 10.3, 7.0 Hz, 1 H, C1-H), 4.66 (d, *J* = 10.3 Hz, 1 H, N-H), 3.96-3.85 (m, 1 H, C2-H), 3.60 (s, 3 H, C18-H), 2.54 (s, 3 H, C16-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.4 (C15), 156.3 (C17), 143.1, 136.0, 134.4, 134.0, 132.7, 129.0, 128.8, 128.3, 128.2, 127.9, 126.4, 125.4, 52.6 (C1), 52.1 (C18), 44.6 (C2), 26.3 (C16).



2.46

Methyl *N*-[*cis*-1,2-dihydro-2-(3-ethoxycarbonylphenyl)-1-naphthyl]carbamate (2.46) [Notebook CLC3-37]. 25% EtOAc/hexanes; pale yellow solid; mp 126-127 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93-7.86 (m, 1 H), 7.80 (s, 1 H), 7.33-7.13 (comp, 6 H), 6.71 (dd, *J* = 9.6, 1.6 Hz, 1 H), 6.12 (dd, *J* = 9.6, 4.7 Hz, 1 H), 5.31 (dd, *J* = 10.0, 7.1 Hz, 1 H), 4.69 (d, *J* = 10.0 Hz, 1 H), 4.32 (q, *J* = 7.1 Hz, 2 H), 3.96-3.87 (m, 1 H), 3.59 (s, 3 H), 1.34 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.3, 156.5, 138.1, 134.2, 133.2, 132.9, 130.6, 130.2, 129.5, 128.8, 128.5, 128.4, 128.3, 128.0, 126.5, 125.6, 60.9, 52.8, 52.2, 44.7, 14.2; IR ($CDCl_3$) 3337, 2981, 1717, 1522, 1283 cm^{-1}; mass spectrum (CI) *m/z* 352.1541 [$C_{21}H_{22}NO_4$ (M+1) requires 352.1549] (base), 277.

NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.93-7.86 (m, 1 H, C15-H), 7.80 (s, 1 H, C12-H), 7.33-7.13 (comp, 6 H, C5-H, C6-H, C7-H, C8-H, C14-H & C16-H), 6.71 (dd, *J* = 9.6, 1.6 Hz, 1 H, C4-H), 6.12 (dd, *J* = 9.6, 4.7 Hz, 1 H, C3-H), 5.31 (dd, *J* = 10.0, 7.1 Hz, 1 H, C1-H), 4.69 (d, *J* = 10.0 Hz, 1 H, N-H), 4.32 (q, *J* = 7.1 Hz, 2 H, C18-H), 3.96-3.87 (m, 1 H, C2-H), 3.59 (s, 3 H, C21-H), 1.34 (t, *J* = 7.1 Hz, 3 H, C19-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ166.3 (C17), 156.5 (C20), 138.1, 134.2, 133.2, 132.9, 130.6, 130.2, 129.5, 128.8, 128.5, 128.4, 128.3, 128.0, 126.5, 125.6, 60.9 (C18), 52.8 (C1), 52.2 (C21), 44.7 (C2), 14.2 (C19).

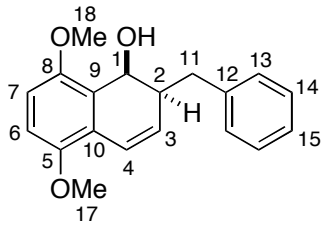


2.51a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(*n*-butyl)-1-naphthol (2.51a) [Notebook CLC2-199].** *n*-BuLi (1.67 mL, 2.20 M solution in pentane, 3.68 mmol) was added to a solution of oxabenzonorbornadiene **2.7a** (150 mg, 0.74 mmol) and TMEDA (222 μL, 1.47 mmol) in THF (7.4 mL) over 5 min at -78 ºC under argon. After 40 min of stirring at -78 ºC, EtOH (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and water (10 mL) and hexane (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with hexane (2 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:5) to give **2.51a** (190 mg, 98%) as a colorless oil. ^{1}H NMR (400 MHz) δ 6.87 (dd, *J* = 9.8, 3.2 Hz, 1 H), 6.78 (d, *J* = 9.0 Hz, 1 H), 6.73 (d, *J* = 9.0 Hz, 1 H), 5.83-5.75 (m, 1 H), 5.02-4.93 (m, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 2.38-2.27 (m, 1 H), 1.94-1.31 (comp, 7 H), 0.94 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (62.5 MHz) δ 150.5, 149.5, 130.8, 125.7, 122.8, 120.6, 111.1, 110.4, 62.6, 56.1, 56.0, 39.8, 29.5, 29.4, 22.9, 14.1; IR ($CDCl_3$) 3596, 2934, 1599, 1483, 1260, 1086 cm^{-1}; mass spectrum (CI) *m/z* 262.1577 [$C_{16}H_{22}O_3$ requires 262.1569], 245 (base), 189 (base).

NMR Assignments. ^{1}H NMR (400 MHz) δ 6.87 (dd, *J* = 9.8, 3.2 Hz, 1 H, C4-H), 6.78 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.73 (d, *J* = 9.0 Hz, 1 H, C7-H), 5.83-5.75 (m, 1 H, C3-H), 5.02-4.93 (m, 1 H, C1-H), 3.82 (s, 3 H, C16-H), 3.78 (s, 3 H, C15-H), 2.38-2.27 (m, 1 H, C2-H), 1.94-1.31 (comp, 7 H, C11-H, C12-H, C13-H & OH), 0.94 (t, *J* = 7.1 Hz, 3 H,

C14-H); ^{13}C NMR (62.5 MHz) δ 150.5, 149.5, 130.8, 125.7, 122.8, 120.6, 111.1, 110.4 (Csp^2), 62.6 (C1), 56.1 (C16), 56.0 (C15), 39.8 (C2), 29.5 (C11 or C12), 29.4 (C11 or C12), 22.9 (C13), 14.1 (C14).

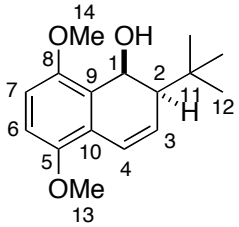


2.53a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-benzyl-1-naphthol (2.53a) [Notebook CLC2-210].** A solution of benzyllithium, which had been generated from *n*-BuLi (0.89 mL, 2.10 M solution in pentane, 1.88 mmol) and toluene (6 mL) containing TMEDA (226 μL) at 0 °C, was added to a solution of oxabenzonorbornadiene **2.7a** (153 mg, 0.75 mmol) in toluene (10 mL) over 1 min at 0 °C under argon. After 3 min of stirring at 0 °C, H_2O (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and water (10 ml) and Et_2O (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:5) to give **2.53a** (194 mg, 87%) as a white solid; mp 89–90 °C; ^{1}H NMR (250 MHz) δ 7.37-7.17 (comp, 5 H), 6.89 (dd, *J* = 9.8, 3.0 Hz, 1 H), 6.77 (d, *J* = 9.0 Hz, 1 H), 6.72 (d, *J* = 9.0 Hz, 1 H), 5.82-5.74 (m, 1 H), 4.88 (ddd, *J* = 7.5, 4.6, 1.6 Hz, 1 H), 3.77 (s, 6 H), 3.18 (dd, *J* = 13.6, 8.3 Hz, 1 H), 2.94 (dd, *J* = 13.6, 8.3 Hz, 1 H), 2.76-2.62 (m, 1 H), 1.62 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (62.5 MHz) δ 150.4, 149.5, 140.3, 129.5, 129.3, 128.4, 126.0, 125.4, 122.7, 121.1, 111.2, 110.4, 62.3, 56.1, 55.9,

41.8, 35.8; IR ($CDCl_3$) 3604, 2939, 1599, 1483, 1260, 1088 cm^{-1}; mass spectrum (CI) *m/z* 296.1413 [$C_{16}H_{22}O_3$ requires 296.1412], 279 (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.37-7.17 (comp, 5 H, C13-H, C14-H & C15-H), 6.89 (dd, *J* = 9.8, 3.0 Hz, 1 H, C4-H), 6.77 (d, *J* = 9.0 Hz, 1 H, C6-H), 6.72 (d, *J* = 9.0 Hz, 1 H, C7-H), 5.82-5.74 (m, 1 H, C3-H), 4.88 (ddd, *J* = 7.5, 4.6, 1.6 Hz, 1 H, C1-H), 3.77 (s, 6 H, C17-H & C18-H), 3.18 (dd, *J* = 13.6, 8.3 Hz, 1 H, C11-H), 2.94 (dd, *J* = 13.6, 8.3 Hz, 1 H, C11-H), 2.76-2.62 (m, C2-H, 1 H), 1.62 (d, *J* = 7.5 Hz, 1 H, OH); ^{13}C NMR (62.5 MHz) δ 150.4, 149.5, 140.3, 129.5, 129.3, 128.4, 126.0, 125.4, 122.7, 121.1, 111.2, 110.4 (Csp^2), 62.3 (C1), 56.1 (C18), 55.9 (C17), 41.8 (C2), 35.8 (C11).

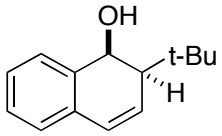


2.54a

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(*tert*-butyl)-1-naphthol (2.54a) [Notebook CLC2-294].** *tert*-BuLi (1.08 mL, 1.70 M solution in pentane, 1.84 mmol) was added to a solution of oxabenzonorbornadiene **2.7a** (150 mg, 0.74 mmol) in THF (7.4 mL) over 5 min at -78 ºC under argon. After 30 min of stirring at -78 ºC, EtOH (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and water (10 mL) and hexane (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with hexane (2 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:5) to give **2.54a** (184 mg, 95%) as a white solid; mp 112-113 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ

6.96 (dd, *J* = 10.0, 3.2 Hz, 1 H), 6.74 (s, 2 H), 6.09-6.01 (m, 1 H), 5.25 (ddd, *J* = 8.5, 4.2, 1.4 Hz, 1 H), 3.82 (s, 3 H), 3.78 (s, 3 H), 2.10-2.04 (m, 1 H), 1.42 (d, *J* = 8.5 Hz, 1 H), 1.17 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 149.9, 149.4, 128.4, 126.1, 122.4, 121.4, 110.8, 110.3, 62.3, 56.1, 55.9, 49.6, 32.3, 28.6; IR ($CDCl_3$) 3590, 2959, 1598, 1482, 1261, 1086 cm^{-1}; mass spectrum (CI) *m/z* 262.1570 [$C_{16}H_{22}O_3$ requires 262.1569], 245, 189 (base).

NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 10.0, 3.2 Hz, 1 H, C4-H), 6.74 (s, 2 H, C6-H & C7-H), 6.09-6.01 (m, 1 H, C3-H), 5.25 (ddd, *J* = 8.5, 4.2, 1.4 Hz, 1 H, C1-H), 3.82 (s, 3 H, C13 or C14-H), 3.78 (s, 3 H, C13 or C14-H), 2.10-2.04 (m, 1 H, C2-H), 1.42 (d, *J* = 8.5 Hz, 1 H, OH), 1.17 (s, 9 H, C12-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 149.9 (C8), 149.4 (C5), 128.4, 126.1, 122.4, 121.4, 110.8, 110.3 (sp^2-C), 62.3 (C1), 56.1 (C14), 55.9 (C13), 49.6 (C2), 32.3 (C11), 28.6 (C12).

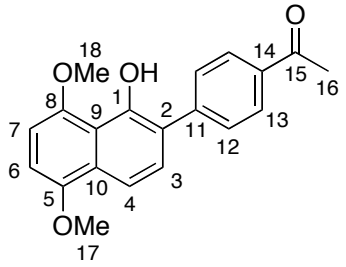


2.55a

***cis*-1,2-Dihydro-2-(*tert*-butyl)-1-naphthol (2.55a) [Notebook CLC2-295].** *tert*-BuLi (1.22 mL, 1.70 M solution in pentane, 2.08 mmol) was added to a solution of oxabenzonorbornadiene **2.7b** (120 mg, 0.83 mmol) in THF (8.3 mL) over 5 min at -78 ºC under argon. After 30 min of stirring at -78 ºC, EtOH (1 mL) was added. The resulting mixture was allowed to warm to room temperature, and water (10 mL) and Et_2O (80 mL) were added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 x 15 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with Et_3N/EtOAc/hexanes (0.1:1:7) to give **2.55a** (157

mg, 93%) as a white solid (mp 75–76 ºC; lit.[72] mp 75 –76 ºC) whose ^{1}H and ^{13}C NMR spectral data were consistent with those reported.[72]

General procedure for IBX oxidation of 2-substituted-1,2-dihydro-1-naphthol. IBX (0.66 mmol) was added to a solution of 2-substituted-1,2-dihydro-1-naphthol (**2.32a**-**2.44a**, **2.51a**, **2.53a**-**2.55a**) (0.22 mmol) in EtOAc (3.3 mL). The resulting suspension was then heated with vigorous stirring in an oil bath at the indicated temperature (see Table 2.7) until the starting material was fully consumed (TLC). The reaction was then allowed to cool to room temperature and diluted with 30% EtOAc/hexanes (15 mL). The mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash chromatography, eluting with EtOAc/hexanes in the ratio given to provide the 2-substituted 1-naphthols (**2.32b**-**2.44b**, **2.51b**, **2.53b**-**2.55b**).

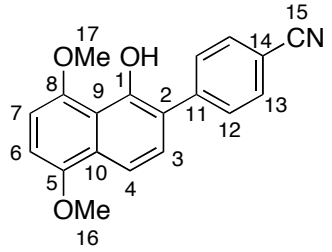


2.32b

5,8-Dimethoxy-2-(4-acetylphenyl)-1-naphthol (2.32b) [Notebook CLC2-186]. 30% EtOAc/hexanes; yellowish solid; mp: 123-124 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.03 (s, 1 H), 8.06-7.99 (m, 2 H), 7.82-7.73 (comp, 3 H), 7.44 (d, *J* = 8.7 Hz, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 6.68 (d, *J* = 8.5 Hz, 1 H), 4.02 (s, 3 H), 3.95 (s, 3 H), 2.63 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 197.9, 151.3, 150.3, 150.2, 143.9, 135.2, 129.8, 128.7,

128.1, 128.0, 122.4, 115.7, 113.3, 104.3, 103.6, 56.6, 55.8, 26.6; IR ($CDCl_3$) 3348, 2946, 1680, 1599, 1392, 1252 cm^{-1}; mass spectrum (CI) *m/z* 323.1285 [$C_{20}H_{19}O_4$ (M+1) requires 323.1283] (base), 307, 154.

NMR Assignments. ^{1}H NMR (250 MHz) δ 10.03 (s, 1 H, OH), 8.06-7.99 (m, 2 H, C13-H), 7.82-7.73 (comp, 3 H, C12-H & C3-H), 7.44 (d, *J* = 8.7 Hz, 1 H, C4-H), 6.74 (d, *J* = 8.5 Hz, 1 H, C6-H), 6.68 (d, *J* = 8.5 Hz, 1 H, C7-H), 4.02 (s, 3 H, C18-H), 3.95 (s, 3 H, C17-H), 2.63 (s, 3 H, C16-H); ^{13}C NMR (62.5 MHz) δ 197.9 (C15), 151.3, 150.3, 150.2, 143.9, 135.2, 129.8, 128.7, 128.1, 128.0, 122.4, 115.7, 113.3, 104.3, 103.6 (Csp^2), 56.6 (C18), 55.8 (C17), 26.6 (C16).

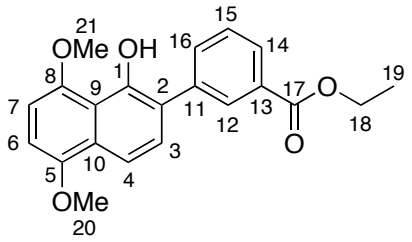


2.33b

5,8-Dimethoxy-2-(4-cyanophenyl)-1-naphthol (2.33b) [Notebook CLC2-195]. 30% EtOAc/hexanes; light yellowish solid; mp: 202-203 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 7.82-7.65 (comp, 5 H), 7.39 (d, *J* = 8.7 Hz, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 6.69 (d, *J* = 8.5 Hz, 1 H), 4.02 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.4, 150.3, 150.2, 143.7, 131.7, 130.3, 128.3, 128.1, 121.5, 119.3, 115.7, 113.5, 109.9, 104.5, 103.8, 56.6, 55.8; IR ($CDCl_3$) 3343, 2926, 1602, 1516, 1392, 1252 cm^{-1}; mass spectrum (CI) *m/z* 306.1133 [$C_{19}H_{16}NO_3$ (M+1) requires 306.1130] (base), 276.

NMR Assignments. ^{1}H NMR (250 MHz) δ 10.06 (s, 1 H, OH), 7.82-7.65 (comp, 5 H, C12-H, C3-H & C13-H), 7.39 (d, *J* = 8.7 Hz, 1 H, C4-H), 6.74 (d, *J* = 8.5 Hz, 1 H, C6-H), 6.69 (d, *J* = 8.5 Hz, 1 H, C7-H), 4.02 (s, 3 H, C18-H), 3.95 (s, 3 H, C17-H); ^{13}C

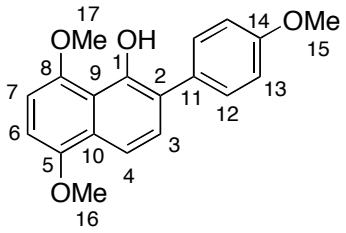
NMR (62.5 MHz) δ 151.4, 150.3, 150.2, 143.7, 131.7, 130.3, 128.3, 128.1, 121.5, 119.3, 115.7, 113.5, 109.9, 104.5, 103.8 (Csp^2 & C15), 56.6 (C17), 55.8 (C16).



2.34b

5,8-Dimethoxy-2-(3-ethoxycarbonylphenyl)-1-naphthol (2.34b) [Notebook CLC2-170]. 30% EtOAc/hexanes; yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.98 (s, 1 H), 8.39-8.32 (m, 1 H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.90-7.83 (m, 1 H), 7.77 (d, *J* = 8.7 Hz, 1 H), 7.57-7.42 (comp, 2 H), 6.71 (d, *J* = 8.4 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 4.38 (q, *J* = 7.1 Hz, 2 H), 4.00 (s, 3 H), 3.95 (s, 3 H), 1.39 (t, *J* = 7.1 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 166.8, 151.0, 150.3, 150.2, 139.0, 134.2, 130.8, 130.3, 129.0, 128.0, 127.8, 127.7, 122.7, 115.7, 113.1, 104.2, 103.3, 60.9, 56.5, 55.7, 14.3; IR ($CDCl_3$) 3355, 2939, 1712, 1605, 1510, 1390, 1251 cm^{-1}; mass spectrum (CI) *m/z* 353.1404 [$C_{21}H_{21}O_5$ (M+1) requires 353.1389] (base), 307.

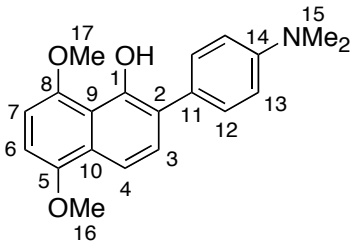
NMR Assignments. ^{1}H NMR (250 MHz) δ 9.98 (s, 1 H, OH), 8.39-8.32 (m, 1 H, C12-H), 8.00 (d, *J* = 7.8 Hz, 1 H, C14-H), 7.90-7.83 (m, 1 H, C16-H), 7.77 (d, *J* = 8.7 Hz, 1 H, C3-H), 7.57-7.42 (comp, 2 H, C15-H & C4-H), 6.71 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.65 (d, *J* = 8.4 Hz, 1 H, C7-H), 4.38 (q, *J* = 7.1 Hz, 2 H, C18-H), 4.00 (s, 3 H, C21-H), 3.95 (s, 3 H, C20-H), 1.39 (t, *J* = 7.1 Hz, 3 H, C19-H); ^{13}C NMR (62.5 MHz) δ 166.8 (C17), 151.0, 150.3, 150.2, 139.0, 134.2, 130.8, 130.3, 129.0, 128.0, 127.8, 127.7, 122.7, 115.7, 113.1, 104.2, 103.3 (Csp^2), 60.9 (C18), 56.5 (C21), 55.7 (C20), 14.3 (C19).



2.35b

5,8-Dimethoxy-2-(4-methoxyphenyl)-1-naphthol (2.35b) [Notebook CLC2-188]. 50% EtOAc/hexanes; a white solid; mp: 114-115 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.92 (s, 1 H), 7.74 (d, *J* = 8.6 Hz, 1 H), 7.62-7.54 (m, 2 H), 7.43 (d, *J* = 8.6 Hz, 1 H), 7.01-6.93 (m, 2 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 3.84 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 158.4, 150.6, 150.2, 150.1, 131.1, 130.7, 129.1, 127.3, 123.3, 115.7, 113.5, 112.9, 104.0, 102.8, 56.4, 55.6, 55.2; IR ($CDCl_3$) 3355, 2939, 1611, 1510, 1390, 1248 cm^{-1}; mass spectrum (CI) *m/z* 311.1286 [$C_{19}H_{19}O_4$ (M+1) requires 311.1283] (base), 295, 260.

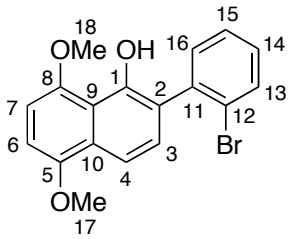
NMR Assignments. ^{1}H NMR (250 MHz) δ 9.92 (s, 1 H, OH), 7.74 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.62-7.54 (m, 2 H, C12-H), 7.43 (d, *J* = 8.6 Hz, 1 H, C4-H), 7.01-6.93 (m, 2 H, C13-H), 6.70 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.63 (d, *J* = 8.4 Hz, 1 H, C7-H), 4.00 (s, 3 H, C17-H), 3.94 (s, 3 H, C16-H), 3.84 (s, 3 H, C15-H); ^{13}C NMR (62.5 MHz) δ 158.4, 150.6, 150.2, 150.1, 131.1, 130.7, 129.1, 127.3, 123.3, 115.7, 113.5, 112.9, 104.0, 102.8 (Csp^2), 56.4 (C15), 55.6 (C17), 55.2 (C16).



2.36b

5,8-Dimethoxy-2-(4-N,N-dimethylanilinyl)-1-naphthol (2.36b) [Notebook CLC2-226]. 50% EtOAc/hexanes; a white solid; mp: 130-131 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.88 (s, 1 H), 7.72 (d, *J* = 8.6 Hz, 1 H), 7.60-7.52 (m, 2 H), 7.46 (d, *J* = 8.6 Hz, 1 H), 6.85-6.79 (m, 2 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 6.61 (d, *J* = 8.4 Hz, 1 H), 4.00 (s, 3 H), 3.94 (s, 3 H), 2.97 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.6, 150.3, 150.2, 149.4, 130.3, 129.3, 127.1, 126.9, 124.0, 115.8, 112.8, 112.4, 103.9, 102.6, 56.5, 55.7, 40.7; IR ($CDCl_3$) 3355, 2926, 1605, 1523, 1390, 1245 cm^{-1}; mass spectrum (CI) *m/z* 324.1598 [$C_{20}H_{22}NO_3$ (M+1) requires 324.1600] (base), 169.

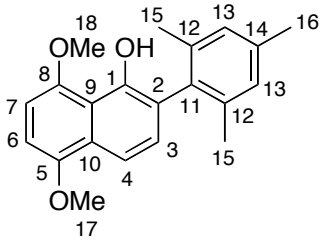
NMR Assignments. ^{1}H NMR (250 MHz) δ 9.88 (s, 1 H, OH), 7.72 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.60-7.52 (m, 2 H, C12-H), 7.46 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.85-6.79 (m, 2 H, C13-H), 6.68 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.61 (d, *J* = 8.4 Hz, 1 H, C7-H), 4.00 (s, 3 H, C17-H), 3.94 (s, 3 H, C16-H), 2.97 (s, 6 H, C15-H); ^{13}C NMR (62.5 MHz) δ 150.6, 150.3, 150.2, 149.4, 130.3, 129.3, 127.1, 126.9, 124.0, 115.8, 112.8, 112.4, 103.9, 102.6 (Csp^2), 56.5 (C17), 55.7 (C16), 40.7 (C15).



2.37b

5,8-Dimethoxy-2-(2-bromophenyl)-1-naphthol (2.37b) [Notebook CLC2-189]. 10% EtOAc/hexanes; yellowish solid; mp: 123-124 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.80 (s, 1 H), 7.76 (d, *J* = 8.6 Hz, 1 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.40-7.16 (comp, 4 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 6.67 (d, *J* = 8.5 Hz, 1 H), 3.98 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.9, 150.3, 150.2, 139.8, 132.6, 131.9, 129.2, 128.7, 128.0, 127.0, 124.3, 123.7, 115.5, 112.4, 103.9, 103.3, 56.4, 55.7; IR ($CDCl_3$) 3355, 2939, 1605, 1510, 1390, 1251 cm^{-1}; mass spectrum (CI) *m/z* 359.0267 [$C_{18}H_{16}O_3Br$ (M+1) requires 359.0283] (base), 280.

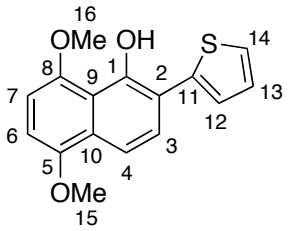
NMR Assignments. ^{1}H NMR (250 MHz) δ 9.80 (s, 1 H, OH), 7.76 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.68 (d, *J* = 8.4 Hz, 1 H, C13-H), 7.40-7.16 (comp, 4 H, C4-H, C14-H, C15-H & C16-H), 6.71 (d, *J* = 8.5 Hz, 1 H, C6-H), 6.67 (d, *J* = 8.5 Hz, 1 H, C7-H), 3.98 (s, 3 H, C18-H), 3.95 (s, 3 H, C17-H); ^{13}C NMR (62.5 MHz) δ 150.9, 150.3, 150.2, 139.8, 132.6, 131.9, 129.2, 128.7, 128.0, 127.0, 124.3, 123.7, 115.5, 112.4, 103.9, 103.3 (Csp^2), 56.4 (C18), 55.7 (C17).



2.38b

5,8-Dimethoxy-2-mesityl-1-naphthol (2.38b) [Notebook CLC3-25]. 10% EtOAc/hexanes; white solid; mp 134-135 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.60 (s, 1 H), 7.76 (d, *J* = 8.5 Hz, 1 H), 7.17 (d, *J* = 8.5 Hz, 1 H), 6.95 (s, 2 H), 6.70 (d, *J* = 8.4 Hz, 1 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 3.98 (s, 3 H), 3.96 (s, 3 H), 2.31 (s, 3 H), 2.02 (s, 6 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.5, 150.3, 150.2, 136.6, 135.1, 129.6, 128.0, 127.6, 123.2, 115.7, 112.8, 103.5, 102.7, 56.3, 55.7, 21.1, 20.3; IR ($CDCl_3$) 3381, 2918, 1612, 1511, 1391, 1252 cm^{-1}; mass spectrum (CI) *m/z* 323.1648 [$C_{21}H_{23}O_3$ (M+1) requires 323.1647] (base).

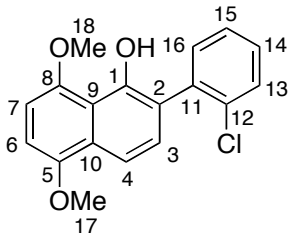
NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.60 (s, 1 H, OH), 7.76 (d, *J* = 8.5 Hz, 1 H, C3-H), 7.17 (d, *J* = 8.5, 1 H, C4-H), 6.95 (s, 2 H, C13-H), 6.70 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.65 (d, *J* = 8.4 Hz, 1 H, C7-H), 3.98 (s, 3 H, C18-H), 3.96 (s, 3 H, C17-H), 2.31 (s, 3 H, C16-H), 2.02 (s, 6H, C15-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.5 (C1), 150.3 (C8), 150.2 (C5), 136.6, 135.1, 129.6, 128.0, 127.6, 123.2, 115.7, 112.8, 103.5, 102.7, 56.3 (C18), 55.7 (C17), 21.1 (C16), 20.3 (C15).



2.39b

5,8-Dimethoxy-2-(2-thienyl)-1-naphthol (2.39b) [Notebook CLC3-60]. 10% EtOAc/hexanes; pale reddish solid; mp 106-107 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.42 (s, 1 H), 7.77 (d, *J* = 8.9 Hz, 1 H), 7.71 (d, *J* = 8.9 Hz, 1 H), 7.63 (dd, *J* = 3.7, 1.1 Hz, 1 H), 7.34 (dd, *J* = 5.0, 1.1 Hz, 1 H), 7.12 (dd, *J* = 5.0, 3.7 Hz, 1 H), 6.72 (d, *J* = 8.5 Hz, 1 H), 6.64 (d, *J* = 8.5 Hz, 1 H), 4.04 (s, 3 H), 3.94 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.3, 150.2, 150.1, 140.0, 127.3, 126.8, 126.7, 125.1, 125.0, 116.7, 116.1, 113.2, 104.4, 103.3, 55.6, 55.7; IR ($CDCl_3$) 3318, 2917, 1611, 1506, 1395, 1251 cm^{-1}; mass spectrum (CI) *m/z* 287.0734 [$C_{16}H_{15}O_3S$ (M+1) requires 287.0742] (base).

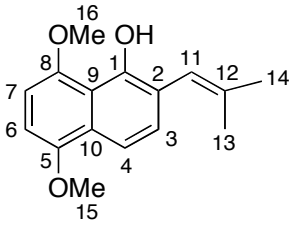
NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.42 (s, 1 H, OH), 7.77 (d, *J* = 8.9 Hz, 1 H, C3-H), 7.71 (d, *J* = 8.9 Hz, 1 H, C4-H), 7.63 (dd, *J* = 3.7, 1.1 Hz, 1 H, C14-H), 7.34 (dd, *J* = 5.0, 1.1 Hz, 1 H, C12-H), 7.12 (dd, *J* = 5.0, 3.7 Hz, 1 H, C13-H), 6.72 (d, *J* = 8.5 Hz, 1 H, C6-H), 6.64 (d, *J* = 8.5 Hz, 1 H, C7-H), 4.04 (s, 3 H, C16-H), 3.94 (s, 3 H, C15-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.3 (C1), 150.2 (C8), 150.1 (C5), 140.0, 127.3, 126.8, 126.7, 125.1, 125.0, 116.7, 116.1, 113.2, 104.4, 103.3 (Ar-C), 55.6 (C16), 55.7 (C15).



2.40b

5,8-Dimethoxy-2-(2-chlorophenyl)-1-naphthol (2.40b) [Notebook CLC2-192]. 10% EtOAc/hexanes; yellowish solid; mp: 104-105 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.83 (s, 1 H), 7.76 (d, *J* = 8.7 Hz, 1 H), 7.53-7.25 (comp, 5 H), 6.71 (d, *J* = 8.5 Hz, 1 H), 6.67 (d, *J* = 8.5 Hz, 1 H), 3.98 (s, 3 H), 3.95 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.1, 150.3, 150.2, 137.7, 133.9, 132.0, 129.4, 129.2, 128.5, 128.0, 126.4, 121.9, 115.5, 112.5, 103.9, 103.3, 56.3, 55.7; IR ($CDCl_3$) 3364, 2939, 1602, 1510, 1390, 1252 cm^{-1}; mass spectrum (CI) *m/z* 315.0789 [$C_{18}H_{16}O_3Cl$ (M+1) requires 315.0788], 186, 154 (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 9.83 (s, 1 H, OH), 7.76 (d, *J* = 8.7 Hz, 1 H, C3-H), 7.53-7.25 (comp, 5 H, C4-H, C13-H, C14-H, C15-H & C16-H), 6.71 (d, *J* = 8.5 Hz, 1 H, C6-H), 6.67 (d, *J* = 8.5 Hz, 1 H, C7-H), 3.98 (s, 3 H, C18-H), 3.95 (s, 3 H, C17-H); ^{13}C NMR (75 MHz) δ 151.1, 150.3, 150.2, 137.7, 133.9, 132.0, 129.4, 129.2, 128.5, 128.0, 126.4, 121.9, 115.5, 112.5, 103.9, 103.3 (Csp^2), 56.3 (C18), 55.7 (C17).

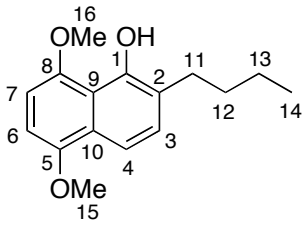


2.41b

5,8-Dimethoxy-2-(2-methyl-propenyl)-1-naphthol (2.41b) [Notebook CLC3-62]. 10% EtOAc/hexanes; orange solid; mp 75-77 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.77

(s, 1 H), 7.64 (d, *J* = 8.6 Hz, 1 H), 7.32 (d, *J* = 8.6 Hz, 1 H), 6.66 (d, *J* = 8.4 Hz, 1 H), 6.59 (d, *J* = 8.4 Hz, 1 H), 6.43 (s, 1 H), 3.99 (s, 3 H), 3.92 (s, 3 H), 1.95 (s, 3 H), 1.82 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.0, 150.3, 150.1, 135.5, 129.2, 126.9, 121.3, 120.6, 115.5, 112.0, 103.7, 102.5, 56.5, 55.7, 26.5, 19.7; IR ($CDCl_3$) 3586, 2937, 1597, 1483, 1259, 1088 cm^{-1}; mass spectrum (CI) *m/z* 259.1329 [$C_{16}H_{19}O_3$ (M+1) requires 259.1334] (base).

NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.77 (s, 1 H, OH), 7.64 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.32 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.66 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.59 (d, *J* = 8.4 Hz, 1 H, C4-H), 6.43 (s, 1 H, C11-H), 3.99 (s, 3 H, C16-H), 3.92 (s, 3 H, C15-H), 1.95 (s, 3 H, C14-H), 1.82 (s, 3 H, C13-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.0 (C1), 150.3 (C16), 150.1 (C15), 135.5, 129.2, 126.9, 121.3, 120.6, 115.5, 112.0, 103.7, 102.5, 56.5 (C16), 55.7 (C15), 26.5 (C14), 19.7 (C13).

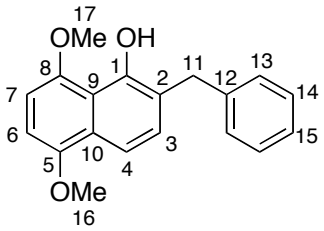


2.51b

5,8-Dimethoxy-2-(*n*-butyl)-1-naphthol (2.51b) [Notebook CLC2-204]. 10% EtOAc/hexanes; yellowish oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.66 (s, 1 H), 7.62 (d, *J* = 8.5 Hz, 1 H), 7.26 (d, *J* = 8.5 Hz, 1 H), 6.64 (d, *J* = 8.4 Hz, 1 H), 6.56 (d, *J* = 8.4 Hz, 1 H), 3.99 (s, 3 H), 3.91 (s, 3 H), 2.74 (t, *J* = 7.6 Hz, 2 H), 1.71-1.54 (m, 2 H), 1.47-1.30 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.1, 150.3, 149.8, 129.3, 126.8, 124.8, 115.4, 112.3, 103.2, 101.9, 56.3, 55.6, 32.1, 29.6, 22.7, 14.1; IR

($CDCl_3$) 3379, 2958, 1613, 1517, 1393, 1252 cm^{-1}; mass spectrum (CI) *m/z* 261.1490 [$C_{16}H_{21}O_3$ (M+1) requires 261.1491] (base), 231, 217.

NMR Assignments. ^{1}H NMR (250 MHz) δ 9.66 (s, 1 H, OH), 7.62 (d, *J* = 8.5 Hz, 1 H, C3-H), 7.26 (d, *J* = 8.5 Hz, 1 H, C4-H), 6.64 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.56 (d, *J* = 8.4 Hz, 1 H, C7-H), 3.99 (s, 3 H, C16-H), 3.91 (s, 3 H, C15-H), 2.74 (t, *J* = 7.6 Hz, 2 H, C11-H), 1.71-1.54 (m, 2 H, C12-H), 1.47-1.30 (m, 2 H, C13-H), 0.93 (t, *J* = 7.3 Hz, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 151.1, 150.3, 149.8, 129.3, 126.8, 124.8, 115.4, 112.3, 103.2, 101.9 (Csp^2), 56.3 (C16), 55.6 (C15), 32.1 (C11), 29.6 (C12), 22.7 (C13), 14.1 (C14).

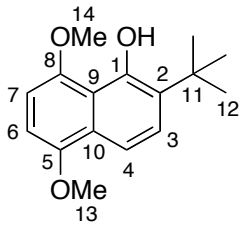


2.53b

5,8-Dimethoxy-2-benzyl-1-naphthol (2.53b) [Notebook CLC2-211]. 10% EtOAc/hexanes; yellowish solid; mp: 107-108 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 9.71 (s, 1 H), 7.63 (d, *J* = 8.5 Hz, 1 H), 7.30-7.09 (comp, 6 H), 6.65 (d, *J* = 8.4 Hz, 1 H), 6.58 (d, *J* = 8.4 Hz, 1 H), 4.11 (s, 2 H), 3.98 (s, 3 H), 3.91 (s, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 151.4, 150.2, 149.9, 141.4, 129.5, 128.7, 128.2, 127.2, 125.7, 122.8, 115.5, 112.6, 103.3, 102.3, 56.2, 55.6, 35.6; IR ($CDCl_3$) 3379, 2941, 1613, 1517, 1393, 1252 cm^{-1}; mass spectrum (CI) *m/z* 295.1338 [$C_{19}H_{19}O_3$ (M+1) requires 295.1334] (base), 217.

NMR Assignments. ^{1}H NMR (400 MHz) δ 9.71 (s, 1 H, OH), 7.63 (d, *J* = 8.5 Hz, 1 H, C3-H), 7.30-7.09 (comp, 6 H, C4, C13, C14 & C15-H), 6.65 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.58 (d, *J* = 8.4 Hz, 1 H, C7-H), 4.11 (s, 2 H, C11-H), 3.98 (s, 3 H, C18-H), 3.91 (s, 3

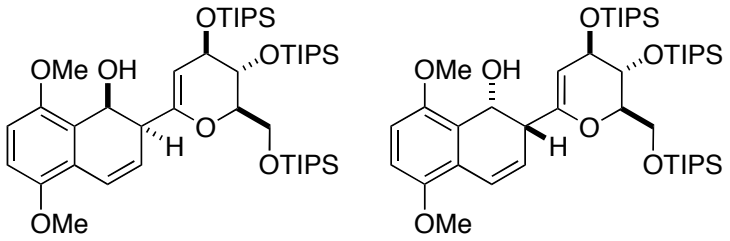
H, C17-H); ^{13}C NMR (100 MHz) δ 151.4, 150.2, 149.9, 141.4, 129.5, 128.7, 128.2, 127.2, 125.7, 122.8, 115.5, 112.6, 103.3, 102.3 (Csp^2), 56.2 (C17), 55.6 (C16), 35.6 (C11).



2.54b

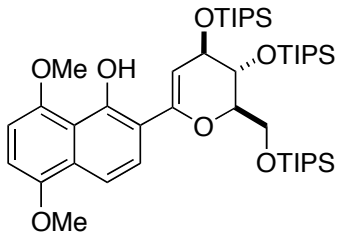
5,8-Dimethoxy-2-(*tert*-butyl)-1-naphthol (2.54b) [Notebook CLC2-296]. 10% EtOAc/hexanes; yellow solid; mp 109-110 ºC; ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 7.61 (d, *J* = 8.9 Hz, 1 H), 7.45 (d, *J* = 8.9 Hz, 1 H), 6.63 (d, *J* = 8.4 Hz, 1 H), 6.55 (d, *J* = 8.4 Hz, 1 H), 4.00 (s, 3 H), 3.91 (s, 3 H), 1.47 (s, 9 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.7, 150.2, 150.1, 131.2, 127.0, 126.0, 116.0, 111.9, 103.2, 101.9, 56.4, 55.7, 34.8, 29.5; IR ($CDCl_3$) 3364, 2958, 1607, 1515, 1399, 1252 cm^{-1}; mass spectrum (CI) *m/z* 261.1491 [$C_{16}H_{21}O_3$ (M+1) requires 261.1491] (base).

NMR Assignments. ^{1}H NMR (250 MHz, $CDCl_3$) δ 10.06 (s, 1 H, OH), 7.61 (d, *J* = 8.9 Hz, 1 H, C3-H), 7.45 (d, *J* = 8.9 Hz, 1 H, C4-H), 6.63 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.55 (d, *J* = 8.4 Hz, 1 H, C7-H), 4.00 (s, 3 H, C14-H), 3.91 (s, 3 H, C13-H), 1.47 (s, 9 H, C12-H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 152.7 (C1), 150.2 (C8), 150.1 (C5), 131.2, 127.0, 126.0, 116.0, 111.9, 103.2, 101.9 (Ar-C), 56.4 (C14), 55.7 (C13), 34.8 (C11), 29.5 (C12).



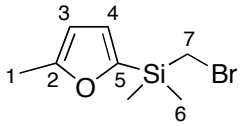
2.8a-**b**

***cis*-1,2-Dihydro-5,8-dimethoxy-2-(1,5-anhydro-3,4,6-*O*-(triisopropylsilyl)-2-deoxy-**D-*arabino*-hex-1-enit-1-yl)-1-naphthol (2.8a**, **2.8b) [Notebook CLC1-88].** A mixture of **2.7a** (83 mg, 0.40 mmol), glycal iodide **2.6** (300 mg, 0.40 mmol), $Pd(OAc)_2$ (14 mg, 0.06 mmol), PPh_3 (32 mg, 0.12 mmol) and activated Zn (265 mg, 4.06 mmol) in a 10 mL round-bottomed flask was purged with argon for three times. DMF (1.5 mL) and PMP (34 μL, 0.19 mmol) were added successively, and the mixtrure was bubbled with argon for 5 min. The reaction was stirred at 65 °C for 12 h. The mixture was cooled to room temperature, and 50% EtOAc/hexanes (20 mL) was added. The mixture was filtered through a celite pad, and washed with brine (4 x 2 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with EtOAc/hexanes (1:40) to give 258 mg (78%) of a mixture (4:1) of diastereomers **2.8a** and **2.8b** as a yellowish oil. The ^1H and ^{13}C NMR spectra were consisted with those reported previously.[90a]



2.9

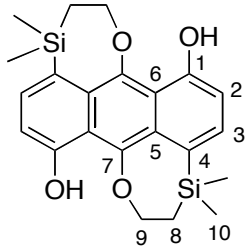
5,8-Dimethoxy-2-(1,5-anhydro-3,4,6-*O*-(triisopropylsilyl)-2-deoxy-D-*arabino*-hex-1-enit-1-yl)-1-naphthol (2.9) [Notebook CLC2-231]. IBX (69 mg, 0.25 mmol) was added to a mixture of alcohol **2.8a** and **2.8b** (67 mg, 0.08 mmol) in EtOAc (1.17 mL), and the reaction was stirred for 8 h at 80 ºC. The mixture was allowed to cooled to room temperature, and 30% EtOAc/hexanes (15 mL) was added. The mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography, eluting with 5% EtOAc/hexanes to give 48 mg (72%) of **2.9** as a yellowish oil. The ^{1}H and ^{13}C NMR spectra were consisted with those reported previously.[90a]



Bromomethyl-dimethyl-(5-methyl-furan-2-yl)silane (4.22) [Notebook CLC6-231]. *n*-BuLi (6.6 mL of a 1.5 M solution in hexanes, 10.0 mmol) was added dropwise to a solution of 2-methylfuran (0.82 g, 10.0 mmol) in THF (20 mL) at 0 °C, and the reaction was stirred for 1 h. Bromomethyldimethylsilane (1.5 mL, 11.0 mmol) was added dropwise over 3 min and stirring continued for 30 min. The mixture was diluted with Et_2O (30 mL) and poured onto a mixture of H_2O (15 mL) and brine (15 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The resulting oil was purified by flash chromatography, eluting with pentane to provide 1.98 g (85%) of silane **4.22** as a

colorless oil; ^{1}H NMR (400 MHz) δ 6.61 (d, *J* = 2.8 Hz, 1 H), 5.96 (dt, *J* = 2.8, 0.8 Hz, 1 H), 2.60 (s, 2 H), 2.31 (d, *J* = 0.8 Hz, 3 H), 0.37 (s, 6 H); ^{13}C NMR (100 MHz) δ 157.3, 154.4, 122.5, 105.9, 16.1, 13.7, -4.3; IR (neat) 2961, 2924, 1593, 1494, 1384, 1252, 1215, 1188, 1018, 812 cm^{-1}; mass spectrum (CI) *m/z* 233.0009 [$C_8H_{14}OSiBr$ (M+1) requires 232.9997], 225 (base).

NMR Assignments. ^{1}H NMR (400 MHz) δ 6.61 (d, *J* = 2.8 Hz, 1 H, C3-H or C4-H), 5.96 (dt, *J* = 2.8, 0.8 Hz, 1 H, C3-H or C4-H), 2.60 (s, 2 H, C7-H), 2.31 (d, *J* = 0.8 Hz, 3 H, C1-H), 0.37 (s, 6 H, C6-H); ^{13}C NMR (100 MHz) δ 157.3, 154.4, 122.5, 105.9, 16.1 (C7), 13.7 (C1), -4.3 (C6).

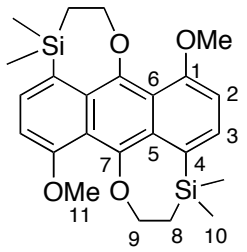


4.87

Anthracenediol (4.87) [Notebook CLC3-179]. A solution of $ZnCl_2$ (2.92 mL of 1 M solution in Et_2O, 2.92 mmol) was added to a solution of **4.42** (571 mg, 1.39 mmol) in CH_2Cl_2 (28 mL) at –78 °C. The reaction was allowed to warm to 0 °C over 1 h, and stirring was continued for 40 min at 0 °C. The mixture was diluted with hexanes (70 mL), washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (15:1) to afford 403 mg (71%) of **4.87** as an orange solid; mp 170-171 °C; ^{1}H NMR (250 MHz) δ 10.53 (s, 2 H), 7.58 (d, *J* = 7.5 Hz, 2 H), 6.84 (d, *J* = 7.5 Hz, 2 H), 5.10-3.98 (br, 4 H), 1.80-1.38 (br, 4 H), 0.44 (s, 12 H); ^{13}C NMR (62.5 MHz) δ 155.8, 152.0, 135.6, 129.5, 123.2, 117.0, 108.6, 78.3, 19.6, 3-0 (br); IR (NaCl) 3402. 2954, 2897, 1579, 1463,

1280, 1251, 1082, 1023 cm^{-1}; mass spectrum (CI) *m/z* 409.1284 [$C_{22}H_{25}O_4Si_2$ requires 409.1291], 383 (base), 367, 354, 339.

NMR Assignments. ^1H NMR (250 MHz) δ 10.53 (s, 2 H, OH), 7.60, (d, *J* = 7.5 Hz, 2 H, C3-H), 6.84 (d, *J* = 7.5 Hz, 2 H, C2-H), 5.10-3.98 (br, 4 H, C9-H), 1.80-1.38 (br, 4 H, C8-H), 0.44 (s, 12 H, C10-H); ^{13}C NMR (62.5 MHz) δ 155.8 (C1), 152.0 (C7), 135.6 (C3), 129.5 (C4), 123.2 (C5), 117.0 (C2), 108.6 (C6), 78.3 (C9), 19.6 (C8), 3-0 (br, C10).

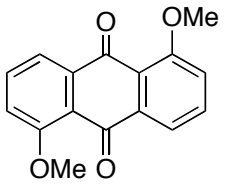


4.88

Anthracenediol dimethyl ether (4.88) [Notebook CLC3-180]. Sodium hydride (235 mg of a 60% suspension in mineral oil, 5.88 mmol) was added to a solution of **4.87** (403 mg, 0.98 mmol) and CH_3I (2.90 g, 20.4 mmol) in DMF (20 mL) at 0 °C. The reaction was allowed to warm to room temperature over 20 min and further stirred for 40 min. The reaction was quenched with H_2O (2 mL), and Et_2O (100 mL) was added. The mixture was washed with brine (4 x 15 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (15:1) to afford 400 mg (93%) of **4.88** as a light orange solid; mp 153-154 °C; ^1H NMR (300 MHz) δ 7.57 (d, *J* = 7.5 Hz, 2 H), 6.75 (d, *J* = 7.5 Hz, 2 H), 5.00-4.60 (br, 2 H), 4.40-4.00 (br, 2 H), 4.01 (s, 6 H), 1.70-1.30 (br, 4 H), 0.41 (s, 12 H); ^{13}C NMR (75 MHz) δ 157.3, 150.9, 133.7, 133.5, 127.9, 118.9, 103.9, 74.6, 56.2, 19.5, 2-(-1); IR (NaCl)

2955, 2896, 1596, 1531, 1384, 1331, 1243, 1073 cm^{-1}; mass spectrum (CI) *m/z* 438.1686 [$C_{24}H_{30}Br_4O_4Si_2$ requires 438.1683], 411, 395, 382 (base).

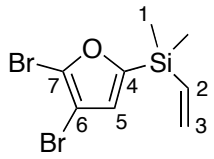
NMR Assignments. ^{1}H NMR (300 MHz) δ 7.57 (d, *J* = 7.5 Hz, 2 H, C3-H), 6.75 (d, *J* = 7.5 Hz, 2 H, C2-H), 5.00-4.60 (br, 2 H, C9-H), 4.40-4.00 (br, 2 H, C9-H), 4.01 (s, 6 H, C11-H), 1.70-1.30 (br, 4 H, C8-H), 0.41 (s, 12 H, C10-H); ^{13}C NMR (75 MHz) δ 157.3 (C1), 150.9 (C7), 133.7 (C3), 133.5 (C4), 127.9 (C5), 118.9 (C2), 103.9 (C6), 74.6 (C9), 56.2 (C11), 19.5 (C8), 2-(-1) (br, C10).



4.89

1,5-Dimethoxyanthra-9,10-quinone (4.89) [Notebook CLC3-145, CLC3-184]. (Procedure 1) BF_3·2AcOH (12.7 μL 0.09 mmol) was added to a solution of **4.88** (10 mg, 0.02 mmol) and $ClCH_2CO_2H$ (8.6 mg, 0.09 mmol) in hexane (0.5 mL). The reaction was stirred for 40 min at room temperature, whereupon EtOAc (7 mL) was added. The mixture was washed with brine (3 x 1 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with $CHCl_3$ to afford 3.5 mg (57 %) of **4.89** as a yellowish solid (mp 234-235 °C; lit.[246] mp 234-235 °C) whose ^{1}H and ^{13}C NMR spectra data were consistent with those reported.[246] (Procedure 2) A solution of **4.88** (73 mg, 0.17 mmol) and TBAF (525 mg, 1.66 mmol) in DMF (3.3 mL) was stirred for 1 h at 70 ºC. The reaction was allowed to cool to room temperature, and 25% EtOAc/hexanes (1:3, 50 mL) was added. The mixture was washed with H_2O (3 x 4 mL) and brine (4 mL), and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with $CHCl_3$ to afford 10 mg

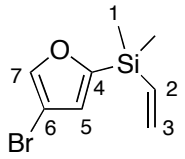
(22 %) of the **4.89** as a yellowish solid (mp 234-235 °C; lit.[246] mp 234-235 °C) whose ^{1}H and ^{13}C NMR spectra data were consistent with those reported.[246]



4.99

Dimethyl(4,5-dibromofuran-2-yl)vinylsilane (4.99) [Notebook CLC3-238]. 2,3-Dibromofuran **(4.98)** (3 g, 13.3 mmol) was added to a solution of LDA (18.6 mmol) in THF (27 mL) at -78 °C, and the reaction was stirred for 1.5 h at -78 °C. Freshly distilled chlorodimethylvinylsilane (4 mL, 26.6 mmol) was added dropwise. The cooling bath was removed, and the mixture was allowed to warm to room temperature. The reaction was stirred for 90 min at room temperature and quenched with H_2O (2 mL). The mixture was added hexanes (200 mL), and washed with water (2 x 20 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by Kugelrohr distillation (200 ºC, 12 torr) and flash chromatography on silica gel, eluting with hexanes to afford 3.94 g (96%) of furan **4.99** as a colorless liquid; ^{1}H NMR (250 MHz) δ 6.63 (s, 1 H), 6.26-6.03 (comp, 2 H), 5.79 (dd, J = 18.8, 5.0 Hz, 1 H), 0.32 (s, 6 H); ^{13}C NMR (62.5 MHz) δ 162.4, 135.0, 134.4, 127.2, 125.3, 101.5, -3.7; IR (NaCl) 3053, 2961, 1466, 1405, 1294, 1252, 1160 cm^{-1}; mass spectrum (CI) *m/z* 307.8875 [$C_8H_{10}Br_2OSi$ requires 307.8868], 117 (base), 149.

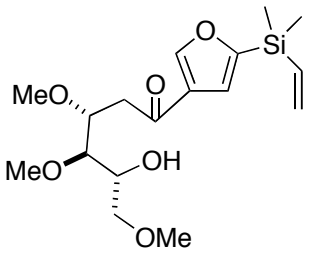
NMR Assignments. ^{1}H NMR (250 MHz) δ 6.63 (s, 1 H, C5-H), 6.26-6.03 (comp, 2 H, C2-H & C3-H), 5.79 (dd, J = 18.8, 5.0 Hz, 1 H, C3-H), 0.32 (s, 6 H, C1-H); ^{13}C NMR (62.5 MHz) δ 162.4, 135.0, 134.4, 127.2, 125.3, 101.5 (C_{sp2}), -3.7 (C1).



4.100

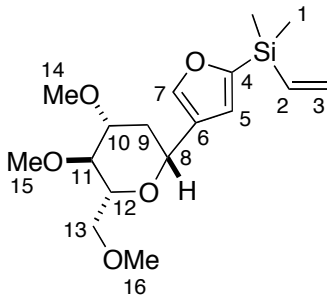
Dimethyl(4-bromofuran-2-yl)vinylsilane (4.100) [Notebook CLC3-239]. *n*-BuLi (5.96 mL, 2.15 M solution in hexanes, 12.8 mmol) was added dropwise to a solution of dibromofuran **4.99** (3.79 g, 12.2 mmol) in Et_2O (49 mL) over 4 min at –78 °C, and the reaction was stirred for 5 min. EtOH (2 mL) was added followed by hexanes (150 mL). The mixture washed with H_2O (2 x 20 mL) and brine (40 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexanes to afford 2.64 g (94%) of furan **4.100** as a colorless oil; ^{1}H NMR (250 MHz) δ 7.60 (s, 1 H), 6.63 (s, 1 H), 6.26-6.01 (comp, 2 H), 5.77 (dd, *J* = 19.3, 4.4 Hz, 1 H), 0.33 (s, 6 H); ^{13}C NMR (62.5 MHz) δ 160.3, 153.9, 145.2, 135.6, 134.0, 123.4, -3.6; IR (NaCl) 3052, 2961, 1405, 1251, 1204, 1110 cm^{-1}; mass spectrum (CI) *m/z* 229.9767 [$C_8H_{11}BrOSi$ requires 229.9762] (base), 117, 149, 163, 195.

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.60 (s, 1 H, C7-H), 6.63 (s, 1 H, C5-H), 6.26-6.01 (comp, 2 H, C2-H & C3-H), 5.77 (dd, *J* = 19.3, 4.4 Hz, 1 H, C3-H), 0.33 (s, 6 H, C1-H); ^{13}C NMR (62.5 MHz) δ 160.3, 153.9, 145.2, 135.6, 134.0, 123.4 (C_{sp2}), -3.6 (C1).



4.102

(3*R*,4*R*,5*R*)-5-hydroxy-3,4,6-trimethoxy-1-(5-(dimethyl(vinyl)silyl)furan-3-yl)hexan-1-one (4.102) [Notebook CLC3-280]. *n*-BuLi (2.83 mL, 2.15 M solution in hexanes, 6.1 mmol) was added dropwise to a solution of 3-bromofuran **4.100** (1.34 g, 5.8 mmol) in THF (29 mL) over 3 min at –78 °C, and the reaction was stirred for 20 min. A solution of lactone **4.101** (1.18 g, 5.8 mmol) in THF (5 mL) was added dropwise over 3 min at –78 °C, and the reaction was stirred for 45 min. The mixture was poured onto saturated $NaHCO_3$ (4 mL) and Et_2O (50 mL), and washed with brine (2 x 10 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford 1.94 g (94%) of **4.102** as a colorless oil. The crude product thus obtained was used for the next step.

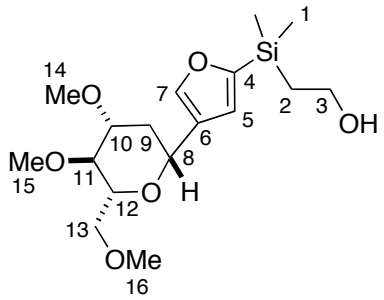


4.104

(2*R*,4*R*,5*R*,6*R*)-[4-(4,5-dimethoxy-6-(methoxymethyl)-tetrahydropyran-2-yl) furan-2-yl)]dimethyl vinylsilane (4.104) [Notebook CLC3-275]. A solution of HCl (3 μL, 0.25 equiv, prepared by addition of 1 mL of AcCl to 10 mL of EtOH) was added to a solution of **4.102** (58 mg, 0.163 mmol) and bromocresol (1 mg) in EtOH (2 mL), and the

reaction was stirred for 1.5 min at room temperature. Another portion of HCl solution (124 μL, 1.08 equiv, prepared by addition of 1 mL of AcCl to 10 mL of EtOH) and $NaBH_3CN$ (20 mg, 0.325 mmol) were added. The reaction was stirred for 1.5 min, and saturated $NaHCO_3$ (2 mL) and EtOAc (20 mL) were added. The organic layer was washed with brine (2 x 2 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (10:1) to afford 29 mg (52%) of glycosylfuran **4.104** as a yellowish liquid; ^{1}H NMR (250 MHz) δ 7.57 (s, 1 H), 6.65, (s, 1 H), 6.26-5.98 (comp, 2 H), 5.75 (dd, *J* = 19.8, 4.2 Hz, 1 H), 4.35 (dd, *J* = 11.7, 1.8 Hz, 1 H), 3.64-3.57 (comp, 2 H), 3.54 (s, 3 H), 3.47-3.32 (comp, 2 H), 3.44 (s, 3 H), 3.38 (s, 3 H), 3.12 (app t, *J* = 9.1, Hz, 1 H), 2.29 (ddd, *J* = 12.9, 4.9, 1.8 Hz, 1H), 1.70-1.55 (m, 1 H), 0.29 (s, 6 H); ^{13}C NMR (62.5 MHz) δ 159.1, 143.9, 136.2, 133.3, 125.8, 119.8, 82.3, 79.9, 79.1, 71.2, 70.4, 60.5, 59.2, 56.9, 36.8, -3.5; IR (NaCl) 2928, 2826, 1455, 1402, 1379, 1250, 1185, 1109, 1082 cm^{-1}; mass spectrum (CI) *m/z* 341.1764 [$C_{17}H_{28}O_5Si$ (M+1) requires 341.1784], 323, 309(base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.57 (s, 1 H, C7-H), 6.65, (s, 1 H, C5-H), 6.26-5.98 (comp, 2 H, C2-H & C3-H), 5.75 (dd, *J* = 19.8, 4.2 Hz, 1 H, C3-H), 4.35 (dd, *J* = 11.7, 1.8 Hz, 1 H, C8-H), 3.64-3.57 (comp, 2 H, C13-H), 3.54 (s, 3 H, Sug-OCH_3), 3.47-3.32 (comp, 2 H, C10-H & C12-H), 3.44 (s, 3 H, Sug-OCH_3), 3.38 (s, 3 H, Sug-OCH_3), 3.12 (app t, *J* = 9.1, Hz, 1 H, C11-H), 2.29 (ddd, *J* = 12.9, 4.9, 1.8 Hz, 1H, C9-Heq), 1.70-1.55 (m, 1 H, C9-Hax), 0.29 (s, 6 H, C1-H); ^{13}C NMR (62.5 MHz) δ 159.1, 143.9, 136.2, 133.3, 125.8, 119.8 (C_{sp2}), 82.3 (C11), 79.9 (C12), 79.1 (C13), 71.2 (C10), 70.4 (C8), 60.5 (OMe), 59.2 (OMe), 56.9 (OMe), 36.8 (C9), -3.5 (C1).

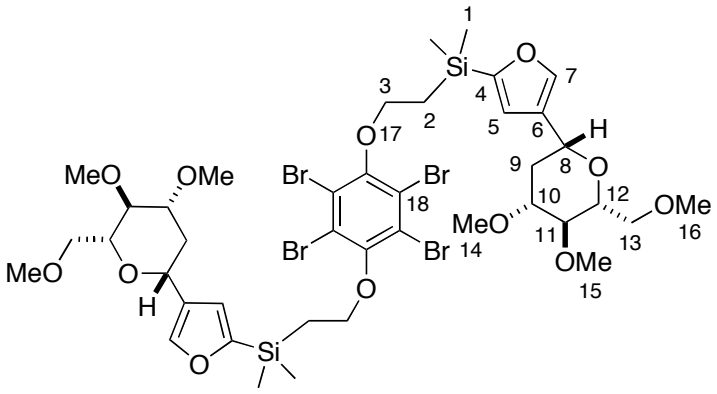


4.105

(2*R*,4*R*,5*R*,6*R*)-2-{[4-(4,5-dimethoxy-6-(methoxymethyl)-tetrahydropyran -2-yl)furan-2-yl)]dimethylsilanyl}ethanol (4.105) [Notebook CLC3-287]. 9-BBN (859 mg, 7.04 mmol) was added to a solution of vinylsilane **4.104** (1.2 g, 3.52 mmol) in THF (28 mL), and the mixture was stirred for 12 h at room temperature. The reaction was cooled to 0 °C, and 1.5 N NaOH (10 mL) was added followed by 30 % H_2O_2 (10 mL). After vigorously stirring for 30 min, Et_2O (200 mL) was added. The mixture was washed with brine (2 x 20 mL), and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (1:1) to afford 957 mg (76 %) of alcohol **4.105** as a yellowish liquid; ^{1}H NMR (250 MHz) δ 7.56 (s, 1 H), 6.65 (s, 1 H), 4.34 (dd, *J* = 11.7, 1.7 Hz, 1 H), 3.75 (t, *J* = 8.1 Hz, 2 H), 3.64-3.58 (comp, 2 H), 3.54 (s, 3 H), 3.48-3.30 (comp, 2 H), 3.44 (s, 3 H), 3.38 (s, 3 H), 3.12 (app t, *J* = 9.2, Hz, 1 H), 2.29 (ddd, *J* = 12.8, 4.9, 1.7 Hz, 1 H), 1.70-1.42 (comp, 2 H), 1.34 (t, *J* = 8.1 Hz, 2 H), 0.23 (s, 6 H); ^{13}C NMR (62.5 MHz) δ 159.5, 143.8, 125.8, 119.6, 82.5, 79.9, 79.1, 72.0, 70.4, 60.6, 59.7, 59.3, 56.9, 36.8, 20.5, -3.15; IR (NaCl) 3437, 2926, 235, 1249, 1109, 1079, 1038 cm^{-1}; mass spectrum (CI) *m/z* 359.1861 [$C_{17}H_{28}O_5Si$ (M+1) requires 359.1890], 327, 225, 186, 155 (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.56 (s, 1 H, C7-H), 6.65 (s, 1 H, C5-H), 4.34 (dd, *J* = 11.7, 1.7 Hz, 1 H, C8-H), 3.75 (t, *J* = 8.1 Hz, 2 H, C3-H), 3.64-3.58 (comp, 2 H, C13-H), 3.54 (s, 3 H, Sug-OCH_3), 3.48-3.30 (comp, 2 H, C10-H & C12-H),

3.44 (s, 3 H, Sug-OCH_3), 3.38 (s, 3 H, Sug-OCH_3), 3.12 (app t, J = 9.2, Hz, 1 H, C11-H), 2.29 (ddd, J = 12.8, 4.9, 1.7 Hz, 1 H, C9-Heq), 1.70-1.42 (comp, 2 H, C9-Hax & OH), 1.34 (t, J = 8.1 Hz, 2 H, C2-H), 0.23 (s, 6 H, C1-H); ^{13}C NMR (62.5 MHz) δ 159.5, 143.8, 125.8, 119.6 (C_{sp2}), 82.5 (C11), 79.9 (C12), 79.1 (C13), 72.0 (C10), 70.4 (C8), 60.6 (OMe), 59.7 (C3), 59.3 (OMe), 56.9 (OMe), 36.8 (C9), 20.5 (C2), -3.15 (C1).

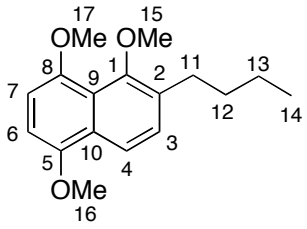


4.106

2,3,5,6-tetrabromo-1,2-bis-(2*R*,4*R*,5*R*,6*R*)-2-{[4-(4,5-dimethoxy-6-(methoxy-methyl)-tetrahydropyran-2-yl)furan-2-yl)]dimethylsilanyl}ethoxy-benzene (4.106) [Notebook CLC3-292]. DIAD (344 mg, 1.70 mmol) was added to a solution of tetrabromohydroquinone (362 mg, 0.85 mmol), alcohol **4.105** (610 mg, 1.70 mmol) and PPh_3 (446 mg, 1.70 mmol) in THF (17 mL), and reaction was stirred for 3 h at room temperature. The mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (1:1) to furnish 612 mg (65%) of arylether **4.106** as a yellowish liquid; ^{1}H NMR (250 MHz) δ 7.56 (s, 1 H), 6.67, (s, 1 H), 4.34 (dd, J = 11.8, 1.7 Hz, 1 H), 4.05 (t, J = 8.4 Hz, 2 H), 3.68-3.56 (comp, 2 H), 3.54 (s, 3 H), 3.48-3.30 (comp, 2 H), 3.44 (s, 3 H), 3.38 (s, 3 H), 3.12 (app t, J = 9.1, Hz, 1 H), 2.29 (ddd, J = 12.9, 4.9, 1.7 Hz, 1H), 1.68-1.54 (m, 1 H), 1.48 (t, J = 8.4 Hz, 2 H), 0.28 (s, 6 H); ^{13}C NMR (62.5 MHz) δ 158.9, 151.9, 143.9, 125.8, 121.5,

119.9, 82.4, 79.9, 79.1, 72.0, 71.2, 70.4, 60.6, 59.3, 56.9, 36.8, 17.4, -3.1; IR (NaCl) 2935, 2890, 2824, 1409, 1342, 1248, 1110, 1082 cm^{-1}; mass spectrum (CI) *m/z* 1107 (base) [$C_{40}H_{59}Br_4O_{12}Si_2$ (M+1) requires 1107.0238], 1049, 850.

NMR Assignments. ^1H NMR (250 MHz) δ 7.56 (s, 1 H, C7-H), 6.67, (s, 1 H, C5-H), 4.34 (dd, *J* = 11.8, 1.7 Hz, 1 H, C8-H), 4.05 (t, *J* = 8.4 Hz, 2 H, C3-H), 3.68-3.56 (comp, 2 H, C13-H), 3.54 (s, 3 H, Sug-OCH_3), 3.48-3.30 (comp, 2 H, C10-H & C12-H), 3.44 (s, 3 H, Sug-OCH_3), 3.38 (s, 3 H, Sug-OCH_3), 3.12 (app t, *J* = 9.1, Hz, 1 H, C11-H), 2.29 (ddd, *J* = 12.9, 4.9, 1.7 Hz, 1H, C9-Heq), 1.68-1.54 (m, 1 H, C9-Hax), 1.48 (t, *J* = 8.4 Hz, 2 H, C2-H), 0.28 (s, 6 H, C1-H); ^{13}C NMR (62.5 MHz) δ 158.9, 151.9 (C17), 143.9, 125.8, 121.5 (C18), 119.9 (C_{sp2}), 82.4 (C11), 79.9 (C12), 79.1 (C13), 72.0 (C10), 71.2 (C3), 70.4 (C8), 60.6 (OMe), 59.3 (OMe), 56.9 (OMe), 36.8 (C9), 17.4 (C2), -3.1 (C1).

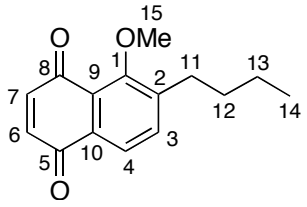


4.116

2-Butyl-1,5,8-trimethoxynaphthalene (4.116) [Notebook CLC4-273]. Sodium hydride (60% dispersion in mineral oil) (1.00 g, 25.8 mmol) was added to a solution of naphthol **4.115** (1.12 g, 4.3 mmol) and methyl iodide (0.80 mL, 12.9 mmol) in DMF (29 mL), and the mixture was stirred for 1 h at room temperature. The reaction was quenched with H_2O (4 mL), and a mixture of 20% ether/hexanes (200 mL) was added. The organic layer was washed with brine (4 x 40 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (8:1) to

afford 1.02 g (97%) of **4.116** as a yellowish oil. ^{1}H NMR (250 MHz) δ 7.94 (d, *J* = 8.6 Hz, 1 H), 7.31 (d, *J* = 8.6 Hz, 1 H), 6.74 (d, *J* = 8.5 Hz, 1 H), 6.65 (d, *J* = 8.5 Hz, 1 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 2.77 (t, *J* = 7.8 Hz, 2 H), 1.72-1.57 (m, 2 H), 1.47-1.31 (m, 2 H), 0.92 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz) δ 153.1, 149.5, 149.3, 133.1, 128.0, 127.3, 120.8, 117.7, 105.7, 102.6, 62.0, 56.4, 55.3, 33.1, 29.3, 22.6, 13.8; IR (NaCl) 2951, 2929, 2858, 2831, 1601, 1581, 1512, 1461, 1411, 1350, 1260, 1065 cm^{-1}; mass spectrum (CI) *m/z* 275 [$C_{17}H_{23}O_3$ (M+1) requires 275.1642] (base).

NMR Assignments. ^{1}H NMR (250 MHz) δ 7.94 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.31 (d, *J* = 8.6 Hz, 1 H, C4-H), 6.74 (d, *J* = 8.5 Hz, 1 H, C6-H), 6.65 (d, *J* = 8.5 Hz, 1 H, C7-H), 3.93 (s, 3 H, OMe), 3.92 (s, 3 H, OMe), 3.79 (s, 3 H, OMe), 2.77 (t, *J* = 7.8 Hz, 2 H, C11-H), 1.72-1.57 (m, 2 H, C12-H), 1.47-1.31 (m, 2 H, C13-H), 0.92 (t, *J* = 7.3 Hz, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 153.1, 149.5, 149.3, 133.1, 128.0, 127.3, 120.8, 117.7, 105.7, 102.6 (Ar-C), 62.0 (OCH_3), 56.4 (OCH_3), 55.3 (OCH_3), 33.1 (C11), 29.3 (C12), 22.6 (C13), 13.8 (C14).

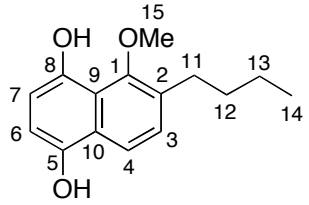


4.117

6-Butyl-5-methoxynaphthalene-1,4-dione (4.117) [Notebook CLC4-21]. A solution of ammonium ceric nitrate (1.24 g, 2.27 mmol) in H_2O (4.7 mL) was added to a solution of **4.116** (259 mg, 0.94 mmol) in CH_3CN (4.7 mL), and the reaction was stirred for 20 min at 0 ºC. A mixture of 50% ether/hexanes (50 mL) was added. The organic layer was washed with brine (4 x 10 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (8:1) to

afford 230 mg (100%) of **4.117** as a yellowish oil. ^{1}H NMR (400 MHz) δ 7.68 (d, *J* = 8.0 Hz, 1 H), 7.44 (d, *J* = 8.0 Hz, 1 H), 6.75 (d, *J* = 10.0 Hz, 1 H), 6.72 (d, *J* = 10.0 Hz, 1 H), 3.74 (s, 3 H), 2.61 (t, *J* = 7.8 Hz, 2 H), 1.52-1.42 (m, 2 H), 1.33-1.21 (m, 2 H), 0.81 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 184.5, 184.3, 158.0, 145.1, 140.0, 136.4, 135.1, 131.8, 123.5, 122.4, 61.5, 32.1, 29.6, 22.4, 13.6; IR (NaCl) 2957, 2935, 2857, 1666, 1611, 1593, 1587, 1467, 1324, 1296, 1252, 1020 cm^{-1}; mass spectrum (CI) *m/z* 245 [$C_{15}H_{17}O_3$ (M+1) requires 245.1178] (base).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.68 (d, *J* = 8.0 Hz, 1 H, C3-H), 7.44 (d, *J* = 8.0 Hz, 1 H, C4-H), 6.75 (d, *J* = 10.0 Hz, 1 H, C7-H), 6.72 (d, *J* = 10.0 Hz, 1 H, C6-H), 3.74 (s, 3 H, C15-H), 2.61 (t, *J* = 7.8 Hz, 2 H, C11-H), 1.52-1.42 (m, 2 H, C12-H), 1.33-1.21 (m, 2 H, C13-H), 0.81 (t, *J* = 7.2 Hz, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 184.5 (C5), 184.3 (C8), 158.0, 145.1, 140.0, 136.4, 135.1, 131.8, 123.5, 122.4 (Ar-C), 61.5 (C15), 32.1 (C11), 29.6 (C12), 22.4 (C13), 13.6 (C14).

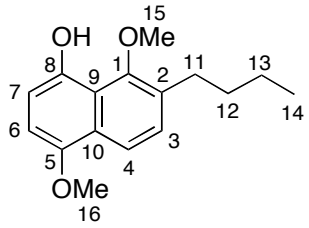


4.128

6-Butyl-5-methoxynaphthalene-1,4-diol (4.128) [Notebook CLC4-275]. A solution of $Na_2S_2O_4$ (1.74 g, 10.0 mmol) in H_2O (5 mL) was added to a solution of quinone **4.117** (244 mg, 1.0 mmol) in 50% THF/ether (10 mL), and the reaction was stirred for 1 h at room temperature. A mixture of 50% ether/hexanes (50 mL) was added. The organic layer was washed with brine (4 x 10 mL), dried ($MgSO_4$) and concentrated to afford 230 mg (100%) of **4.128** as a yellowish oil. ^{1}H NMR (300 MHz) δ 9.22 (s, 1 H), 7.92 (d, *J* = 8.7 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1 H), 6.76 (d, *J* = 8.1 Hz, 1 H), 6.72 (d, *J* =

8.1 Hz, 1 H), 5.09 (br, 1 H), 3.93 (s, 3 H), 2.81 (t, *J* = 7.8 Hz, 2 H), 1.76-1.64 (m, 2 H), 1.53-1.40 (m, 2 H), 0.99 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz) δ 152.6, 146.0, 144.8, 130.5, 127.4, 125.7, 119.2, 117.6, 109.5, 109.2, 62.9, 32.6, 28.5, 22.6, 13.8; IR (NaCl) 3374, 2956, 2930, 2860, 1607, 1469, 1404, 1317, 1252, 1216, 1000 cm^{-1}; mass spectrum (CI) *m/z* 247 [$C_{15}H_{19}O_3$ (M+1) requires 247.1334] (base).

NMR Assignments. ^{1}H NMR (300 MHz) δ 9.22 (s, 1 H, C8-OH), 7.92 (d, *J* = 8.7 Hz, 1 H, C3-H), 7.33 (d, *J* = 8.7 Hz, 1 H, C4-H), 6.76 (d, *J* = 8.1 Hz, 1 H, C6-H), 6.72 (d, *J* = 8.1 Hz, 1 H, C7-H), 5.09 (br, 1 H, C5-OH), 3.93 (s, 3 H, C15-H), 2.81 (t, *J* = 7.8 Hz, 2 H, C11-H), 1.76-1.64 (m, 2 H, C12-H), 1.53-1.40 (m, 2 H, C13-H), 0.99 (t, *J* = 7.4 Hz, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 152.6, 146.0, 144.8, 130.5, 127.4, 125.7, 119.2, 117.6, 109.5, 109.2 (Ar-C), 62.9 (C15), 32.6 (C11), 28.5 (C12), 22.6 (C13), 13.8 (C14).

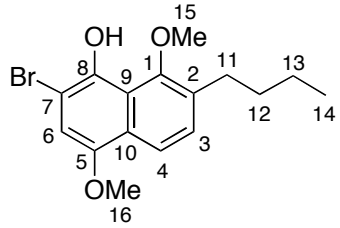


4.129

7-Butyl-4,8-dimethoxynaphthalen-1-ol (4.129) [Notebook CLC4-276]. A solution of hydroquinone **4.128** (230 mg, 0.94 mmol), Me_2SO_4 (353 mg, 2.80 mmol), and K_2CO_3 (388 mg, 2.81 mmol) in acetone (9.4 mL) was stirred for 4 h at 50 ºC under argon. The reaction was allowed to cool to room temperature, and a mixture of 50% EtOAc/hexanes (100 mL) was added. The mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (10:1) to afford 201 mg (83%) of **4.129** as a yellowish oil. ^{1}H NMR (300 MHz) δ 9.13 (s, 1 H), 7.94 (d, *J* = 8.7

Hz, 1 H), 7.27 (d, *J* = 8.7 Hz, 1 H), 6.77 (d, *J* = 8.4 Hz, 1 H), 6.68 (d, *J* = 8.4 Hz, 1 H), 3.91 (s, 3 H), 3.88 (s, 3 H), 2.76 (t, *J* = 7.8 Hz, 2 H), 1.74-1.61 (m, 2 H), 1.49-1.32 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz) δ 152.7, 148.3, 146.6, 130.7, 127.5, 126.4, 119.0, 117.7, 109.0, 104.7, 62.9, 55.5, 32.6, 28.5, 22.6, 13.8; IR (NaCl) 3382, 2956, 2831, 2859, 1608, 1469, 1446, 1404, 1350, 1287, 1255, 1224, 1045 cm^{-1}; mass spectrum (CI) *m/z* 261 [$C_{16}H_{21}O_3$ (M+1) requires 261.1491] (base).

NMR Assignments. ^{1}H NMR (300 MHz) δ 9.13 (s, 1 H, C8-OH), 7.94 (d, *J* = 8.7 Hz, 1 H, C3-H), 7.27 (d, *J* = 8.7 Hz, 1 H, C4-H), 6.77 (d, *J* = 8.4 Hz, 1 H, C6-H), 6.68 (d, *J* = 8.4 Hz, 1 H, C7-H), 3.91 (s, 3 H, OMe), 3.88 (s, 3 H, OMe), 2.76 (t, *J* = 7.8 Hz, 2 H, C11-H), 1.74-1.61 (m, 2 H, C12-H), 1.49-1.32 (m, 2 H, C13-H), 0.94 (t, *J* = 7.4 Hz, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 152.7, 148.3, 146.6, 130.7, 127.5, 126.4, 119.0, 117.7, 109.0, 104.7 (Ar-C), 62.9 (OCH_3), 55.5 (OCH_3), 32.6 (C11), 28.5 (C12), 22.6 (C13), 13.8 (C14).

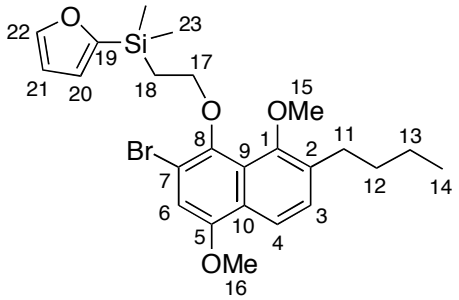


4.130

2-Bromo-7-butyl-4,8-dimethoxynaphthalen-1-ol (4.130) [Notebook CLC4-71]. Bromine (77 μL, 1.49 mmol) was added to a solution of **4.129** (323 mg, 1.24 mmol) in CCl_4 (12.4 mL) under nitrogen at 0 °C, and the mixture was stirred for 5 min. The reaction was quenched with saturated sodium sulfite solution (10 mL), and a mixture of 50% EtOAc/hexanes (50 mL) was added. The organic layer was washed with brine (2 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was

purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (12:1) to afford 412 mg (98%) of **4.130** as a yellowish oil. ^{1}H NMR (300 MHz) δ 9.84 (s, 1 H), 7.90 (d, *J* = 8.7 Hz, 1 H), 7.29 (d, *J* = 8.7 Hz, 1 H), 6.86 (s, 1 H), 3.90 (s, 3 H), 3.89 (s, 3 H), 2.76 (t, *J* = 7.7 Hz, 2 H), 1.73-1.60 (m, 2 H), 1.44-1.31 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz) δ 152.1, 148.4, 143.2, 132.0, 128.1, 125.8, 119.3, 117.9, 108.8, 103.0, 63.3, 55.9, 32.7, 28.7, 22.6, 13.9; IR (NaCl) 3325, 2956, 2931, 2859, 1603, 1446, 1402, 1348, 1289, 1254, 1182, 1045 cm^{-1}; mass spectrum (CI) *m/z* 339 [$C_{16}H_{21}BrO_3$ (M+1) requires 161.1491] (base).

NMR Assignments. ^{1}H NMR (300 MHz) δ 9.84 (s, 1 H, C8-OH), 7.90 (d, *J* = 8.7 Hz, 1 H, C3-H), 7.29 (d, *J* = 8.7 Hz, 1 H, C4-H), 6.86 (s, 1 H, C6-H), 3.90 (s, 3 H, OMe), 3.89 (s, 3 H, OMe), 2.76 (t, *J* = 7.7 Hz, 2 H, C11-H), 1.73-1.60 (m, 2 H, C12-H), 1.44-1.31 (m, 2 H, C13-H), 0.94 (t, *J* = 7.4 Hz, 3 H, C14-H); ^{13}C NMR (100 MHz) δ 152.1, 148.4, 143.2, 132.0, 128.1, 125.8, 119.3, 117.9, 108.8, 103.0 (Ar-C), 63.3 (OCH_3), 55.9 (OCH_3), 32.7 (C11), 28.7 (C12), 22.6 (C13), 13.9 (C14).

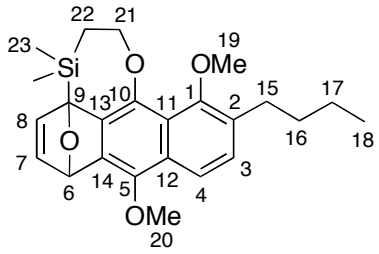


4.131

2-Bromo-7-butyl-4,8-dimethoxy-1-[2-(furanyldimethylsilanyl)]ethoxynaphthalene (4.131) [Notebook CLC4-72]. DIAD (19 mg, 0.09 mmol) was added to a solution of naphthol **4.130** (31 mg, 0.09 mmol), alcohol **4.40** (16 mg, 0.09 mmol) and PPh_3 (24 mg, 0.09 mmol) in THF (1 mL), and the reaction was stirred for 15 min at room

temperature. The mixture was concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (1:40) to afford 23 mg (51%) of **4.131** as a yellowish liquid. ^{1}H NMR (400 MHz) δ 7.91 (d, *J* = 8.8 Hz, 1 H), 7.62-7.61 (m, 1 H) 7.29 (d, *J* = 8.8 Hz, 1 H), 6.87 (s, 1 H), 6.68 (d, *J* = 2.8 Hz, 1 H), 6.35 (dd, *J* = 3.2, 1.4 Hz, 1 H), 4.01 (t, *J* = 8.6 Hz, 2 H), 3.92 (s, 3 H), 3.79 (s, 3 H), 2.79 (t, *J* = 7.8 Hz, 2 H), 1.68-1.54 (m, 4 H), 1.47-1.36 (m, 2 H), 0.94 (t, *J* = 7.4 Hz, 3 H), 0.32 (s, 6 H); ^{13}C NMR (100 MHz) δ 158.6, 152.4, 152.0, 146.7, 144.4, 134.6, 133.8, 126.8, 123.8, 120.1, 118.3, 114.9, 109.3, 107.8, 71.9, 62.9, 55.9, 33.2, 29.4, 22.7, 17.4, 14.0, -3.1; IR (NaCl) 2956, 2929, 1587, 1413, 1322, 1252, 1056, 1005 cm^{-1}; mass spectrum (CI) *m/z* 490 [$C_{24}H_{31}BrO_4Si$ requires 490.1175], 397 (base).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.91 (d, *J* = 8.8 Hz, 1 H, C3-H), 7.62-7.61 (m, 1 H, C22-H) 7.29 (d, *J* = 8.8 Hz, 1 H, C4-H), 6.87 (s, 1 H, C6-H), 6.68 (d, *J* = 3.0 Hz, 1 H, C20-H), 6.35 (dd, *J* = 3.0, 1.4 Hz, 1 H, C21-H), 4.01 (t, *J* = 8.6 Hz, 2 H, C17-H), 3.92 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 2.79 (t, *J* = 7.8 Hz, 2 H, C11-H), 1.68-1.54 (m, 4 H, C12-H & C18-H), 1.47-1.36 (m, 2 H, C13-H), 0.94 (t, *J* = 7.4 Hz, 3 H, C14-H), 0.32 (s, 6 H, C23-H); ^{13}C NMR (100 MHz) δ 158.6, 152.4, 152.0, 146.7, 144.4, 134.6, 133.8, 126.8, 123.8, 120.1, 118.3, 114.9, 109.3, 107.8 (Ar-C), 71.9 (C17), 62.9 (OCH_3), 55.9 (OCH_3), 33.2 (C11), 29.4 (C12), 22.7 (C13), 17.4 (C18), 14.0 (C14), -3.1 (C23).

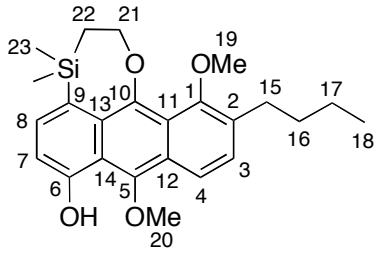


4.122

Cycloadduct (4.122) [Notebook CLC4-78]. A solution of LDA (3.94 mL of a 0.08 M solution in Et_2O, 0.33 mmol) was added dropwise to a solution of **4.131** (23 mg, 0.05 mmol) in Et_2O (0.5 mL) at room temperature over 10 min. Once the addition was complete, the mixture was stirred for 30 min. The reaction was was quenched water (1 mL), and Et_2O (10 mL) was added. The organic layer was washed with brine (2 x 1 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (20:1) to afford 7 mg (36%) of **4.122** as a yellowish oil. ^{1}H NMR (400 MHz) δ 7.82 (d, *J* = 8.6 Hz, 1 H), 7.29 (d, *J* = 8.6 Hz, 1 H), 7.00 (s, 2 H), 6.19 (s, 1 H), 4.69 (dd, *J* = 10.8, 7.5 Hz, 1 H), 4.14 (td, *J* = 12.3, 5.1 Hz, 1 H), 4.04 (s, 3 H), 3.82 (s, 3 H), 2.90-2.63 (m, 2 H), 1.75-1.03 (comp, 6 H), 0.97 (t, *J* = 7.4 Hz), 0.51 (s, 3 H), 0.27 (s, 3 H); ^{13}C NMR (100 MHz) δ 154.0, 144.7, 143.7, 143.2, 140.5, 137.9, 134.2, 129.1, 128.3, 127.6, 122.9, 118.9, 84.9, 82.5, 71.9, 62.8, 60.9, 33.5, 29.5, 23.2, 16.0, 14.3, -3.9, -4.0; IR (NaCl) 2957, 2929, 2871, 1642, 1602, 1454, 1421, 1368, 1333, 1250 cm^{-1}; mass spectrum (CI) *m/z* 411.21 [$C_{24}H_{31}O_4Si$ (M+1) requires 411.1992] (base).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.82 (d, *J* = 8.6 Hz, 1 H, C3-H), 7.29 (d, *J* = 8.6 Hz, 1 H, C4-H), 7.00 (s, 2 H, C7-H & C8-H), 6.19 (s, 1 H, C6-H), 4.69 (dd, *J* = 10.8, 7.5 Hz, 1 H, C21-H), 4.14 (td, *J* = 12.3, 5.1 Hz, 1 H, C21-H), 4.04 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 2.90-2.63 (m, 2 H, C15-H), 1.75-1.03 (comp, 6 H, C16-H, C17-H & C22-H), 0.97 (t, *J* = 7.4 Hz, C18-H), 0.51 (s, 3 H, C23-H), 0.27 (s, 3 H, C23-

H); ^{13}C NMR (100 MHz) δ 154.0, 144.7, 143.7, 143.2, 140.5, 137.9, 134.2, 129.1, 128.3, 127.6, 122.9, 118.9 (Csp2), 84.9 (C6), 82.5 (C9), 71.9 (C21), 62.8 (OCH_3), 60.9 (OCH_3), 33.5 (C15), 29.5 (C16), 23.2 (C17), 16.0 (C22), 14.3 (C18), -3.9 (C23), -4.0 (C23).

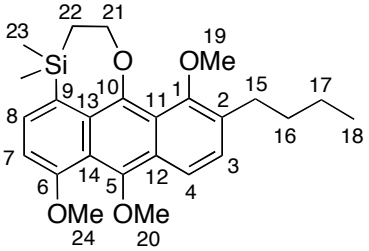


4.123

Anthracene (4.123) [Notebook CLC4-84]. A solution of $ZnCl_2$ in Et_2O (291 μL, 1 M solution, 0.29 mmol) was added to a solution of **4.122** (60 mg, 0.15 mmol) in CH_2Cl_2 (1.4 mL), and the reaction was stirred for 40 min at room temperature. The mixture was diluted with Et_2O (20 mL), and washed with H_2O (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (30:1) to afford 35 mg (58%) of **4.123** as a yellowish liquid. ^{1}H NMR (400 MHz) δ 10.02 (s, 1 H), 7.87 (d, *J* = 9.0 Hz, 1 H), 7.59 (d, *J* = 7.6 Hz, 1 H), 7.33 (d, *J* = 9.0 Hz, 1 H), 6.84 (d, *J* = 7.6 Hz, 1 H), 4.82-4.62 (br, 2 H), 4.06 (s, 3 H), 3.85 (s, 3 H), 2.90-2.73 (br, 2 H), 1.75-1.60 (m, 2 H), 1.60-1.36 (m, 2 H), 1.36-1.20 (m, 2 H), 0.98 (t, *J* = 7.2 Hz, 1 H), 0.43 (s, 6 H); ^{13}C NMR (100 MHz) δ 154.5, 152.6, 147.5, 139.6, 135.1, 133.4, 131.8, 128.5, 126.5, 125.1, 120.8, 117.3, 116.2, 108.1, 74.6, 65.5, 62.2, 33.2, 29.3, 23.0, 19.8, 14.1, -4.0 ; IR (NaCl) 3338, 2955, 2926, 2859, 1731, 1626, 1521, 1520, 1468, 1377, 1339, 1281, 1248, 1051, 1402, 1004, 817 cm^{-1}; mass spectrum (CI) *m/z* 410 [$C_{24}H_{30}O_4Si$ requires 410.1913], 395 (base).

NMR Assignments. ^{1}H NMR (400 MHz) δ 10.02 (s, 1 H, C6-OH), 7.87 (d, *J* = 9.0 Hz, 1 H, C3-H), 7.59 (d, *J* = 7.6 Hz, 1 H, C8-H), 7.33 (d, *J* = 9.0 Hz, 1 H, C4-H),

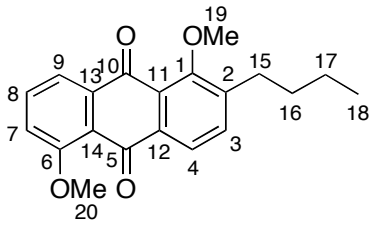
6.84 (d, *J* = 7.6 Hz, 1 H, C7-H), 4.82-4.62 (br, 2 H, C21-H), 4.06 (s, 3 H, OMe), 3.85 (s, 3 H, OMe), 2.90-2.73 (br, 2 H, C15-H), 1.75-1.60 (m, 2 H, C16-H), 1.60-1.36 (m, 2 H, C17-H), 1.36-1.20 (m, 2 H, C22-H), 0.98 (t, *J* = 7.2 Hz, 1 H, C18-H), 0.43 (s, 6 H, C23-H); ^{13}C NMR (100 MHz) δ 154.5, 152.6, 147.5, 139.6, 135.1, 133.4, 131.8, 128.5, 126.5, 125.1, 120.8, 117.3, 116.2, 108.1 (Csp2), 74.6 (C21), 65.5 (OCH_3), 62.2 (OCH_3), 33.2 (C15), 29.3 (C16), 23.0 (C17), 19.8 (C22), 14.1 (C19), -4.0 (br).



4.124

Anthracene (4.124) [Notebook CLC4-85]. Sodium hydride (12 mg of a 60% suspension, 0.31 mmol) was added to a solution of **4.123** (32 mg, 0.078 mmol) and CH_3I (19 μL, 0.310 mmol) in DMF (1.6 mL) at 0 °C. The reaction was allowed to warm to room temperature over 20 min and then stirred for 40 min. The mixture was quenched with H_2O (1 mL), and a mixture of 25% hexanes/EtOAc (25 mL) was added. The organic layer was washed with brine (4 x 3 mL), dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (25:1) to afford 30 mg (91%) of **4.124** as a yellowish oil. ^{1}H NMR (400 MHz) δ 8.10 (d, *J* = 8.8 Hz, 1 H), 7.58 (d, *J* = 7.2 Hz, 1 H), 7.30 (d, *J* = 8.8 Hz, 1 H), 6.75 (d, *J* = 7.2 Hz, 1 H), 4.92-4.72 (br, 2 H), 4.05 (s, 3 H), 3.96 (s, 3 H), 3.84 (s, 3 H), 2.92-2.75 (br, 2 H), 1.78-1.62 (m, 2 H), 1.57-1.40 (m, 2 H), 1.35-1.23 (m, 2 H), 0.98 (t, *J* = 7.2 Hz, 1 H), 0.44 (s, 6 H); mass spectrum (CI) *m/z* 425 [$C_{25}H_{33}O_4Si$ (M+1) requires 425.2148], 397, 429 (base).

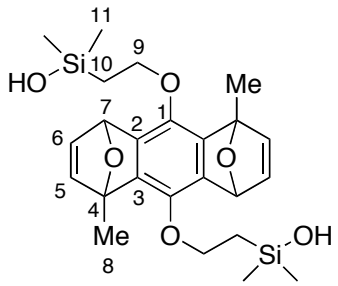
NMR Assignments. ^{1}H NMR (400 MHz) δ 8.10 (d, *J* = 8.8 Hz, 1 H, C3-H), 7.58 (d, *J* = 7.2 Hz, 1 H, C8-H), 7.30 (d, *J* = 8.8 Hz, 1 H, C4-H), 6.75 (d, *J* = 7.2 Hz, 1 H, C7-H), 4.92-4.72 (br, 2 H, C21-H), 4.05 (s, 3 H, OMe), 3.96 (s, 3 H, OMe), 3.84 (s, 3 H, OMe), 2.92-2.75 (br, 2 H, C15-H), 1.78-1.62 (m, 2 H, C16-H), 1.57-1.40 (m, 2 H, C17-H), 1.35-1.23 (m, 2 H, C22-H), 0.98 (t, *J* = 7.2 Hz, 1 H, C18-H), 0.44 (s, 6 H, C23-H).



4.125

2-Butyl-1,5-dimethoxyanthracene-9,10-dione (4.125) [Notebook CLC4-88]. TBAF (100 mg, 0.38 mmol) was added to a solution of **4.124** (30 mg, 0.07 mmol) in DMF (1 mL), and the mixture was stirred for 1 h at 70 ºC. The reaction was allowed to cool to room temperature, and a mixture of 25% EtOAc/Hexane (30 mL) was added. The organic layer was washed with H_2O (3 x 2 mL) and brine (2 x 4 mL). The solution was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with $CHCl_3$ to afford 10 mg (44%) of **4.125** as a yellowish oil. ^{1}H NMR (400 MHz) δ 7.99 (d, *J* = 8.0 Hz, 1 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.68 (t, *J* = 8.2 Hz, 1 H), 7.56 (d, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.0 Hz, 1 H), 4.02 (s, 3 H), 3.91 (s, 3 H), 2.73 (t, *J* = 7.8 Hz, 1 H), 1.65-1.55 (m, 2 H), 1.43-1.33 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz) δ 183.0, 182.6, 159.8, 158.3, 144.0, 137.3, 135.7, 135.4, 134.9, 124.9, 123.3, 121.1, 119.7, 117.0, 61.9, 56.5, 32.5, 29.8, 22.6, 13.9; IR (NaCl) 2956, 2930, 1859, 1670, 1586, 1572, 1467, 1444, 1263 cm^{-1}; mass spectrum (CI) *m/z* 325 [$C_{20}H_{21}O_4$ requires 325.1440] (base).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.99 (d, *J* = 8.0 Hz, 1 H, C3-H), 7.88 (d, *J* = 8.0 Hz, 1 H, C9-H), 7.68 (t, *J* = 8.2 Hz, 1 H, C8-H), 7.56 (d, *J* = 8.0 Hz, 1 H, C7-H), 7.27 (d, *J* = 8.0 Hz, 1 H, C4-H), 4.02 (s, 3 H, OMe), 3.91 (s, 3 H, OMe), 2.73 (t, *J* = 7.8 Hz, 1 H, C15-H), 1.65-1.55 (m, 2 H, C16-H), 1.43-1.33 (m, 2 H, C17-H), 0.93 (t, *J* = 7.2 Hz, 3 H, C18-H); ^{13}C NMR (100 MHz) δ 183.0, 182.6, 159.8, 158.3, 144.0, 137.3, 135.7, 135.4, 134.9, 124.9, 123.3, 121.1, 119.7, 117.0 (Ar-C), 61.9 (OCH_3), 56.5 (OCH_3), 32.5 (C15), 29.8 (C16), 22.6 (C17), 13.9 (C18).

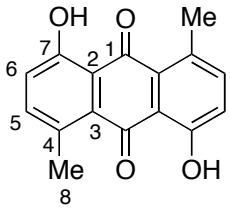


4.137

Cycloadduct (4.137) [Notebook CLC6-115]. Potassium hydroxide (2 pellets) and H_2O (0.3 mL) were added to a solution of cycloadduct **4.33** (80 mg, 0.18 mmol) in DMF (3 mL), and the mixture was stirred for 2 h at room temperature. The mixture was diluted with 50% Et_2O/hexanes (50 mL) and washed with brine (5 x 5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (1:2) to afford 68 mg (79%) of **4.137** as a yellowish oil. ^{1}H NMR (400 MHz) δ 7.02-6.96 (m, 2 H), 6.81 (d, *J* = 5.6 Hz, 2 H), 5.69 (dd, *J* = 4.0, 2.0 Hz, 2 H), 4.05-3.96 (m, 4 H), 1.96 (s, 7 H), 1.62-1.57 (br, 1 H, OH), 1.25-1.12 (m, 4 H), 0.20 (s, 12 H); ^{13}C NMR (125 MHz) δ 146.6, 146.4, 144.1, 144.0, 143.5, 143.3, 142.7, 142.7, 142.1, 141.9, 90.1, 80.2, 80.2, 72.0, 71.6,

19.8, 19.8, 16.9, 16.9, 0.3, 0.3; IR (neat) 3388, 2915, 2853, 1463, 1249 cm^{-1}; mass spectrum (CI) *m/z* 474.1874 [$C_{24}H_{34}O_6Si_2$ requires 474.1894].

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.02-6.96 (m, 2 H, C6-H), 6.81 (d, *J* = 5.6 Hz, 2 H, C5-H), 5.69 (dd, *J* = 4.0, 2.0 Hz, 2 H, C7-H), 4.05-3.96 (m, 4 H, C9-H), 1.96 (s, 7 H, C8-H & OH), 1.62-1.57 (br, 1 H, OH), 1.25-1.12 (m, 4 H, C10-H), 0.20 (s, 12 H, C11-H); ^{13}C NMR (125 MHz) δ 146.6, 146.4, 144.1, 144.0, 143.5, 143.3, 142.7, 142.7, 142.1, 141.9, 90.1, 80.2, 80.2, 72.0, 71.6, 19.8 (C8), 19.8 (C8), 16.9 (C10), 16.9 (C10), 0.3 (C11), 0.3 (C11).

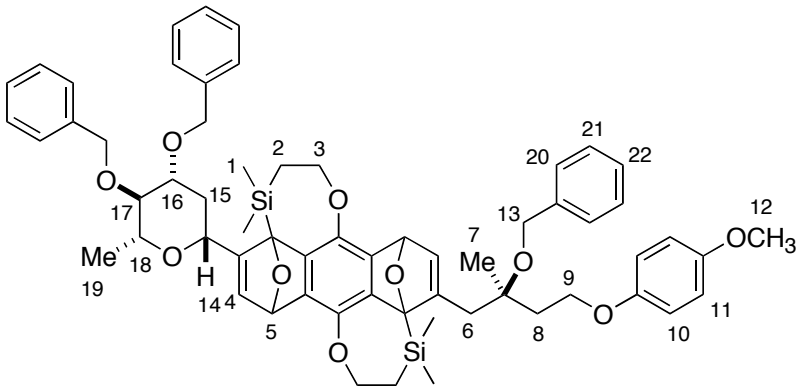


4.37

5.2.7. 1,5-Dihydroxy-4,8-dimethylanthraquinone (4.37) [Notebook CLC6-116]. Cycloadduct **4.137** (68 mg, 0.14 mmol) in MeOH (4 mL) containing concentrated HCl (5 drop) was stirred in air for 3 h at 75 °C. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (10:1) to afford 28 mg (73%) of **4.37** as a reddish solid; mp 237-238 °C; ^{1}H NMR (500 MHz) δ 13.40 (s, 2 H), 7.43 (d, *J* = 8.7 Hz, 2 H), 7.19 (d, *J* = 8.7 Hz, 2 H), 2.72 (s, 6 H); ^{13}C NMR (125 MHz) δ 190.6, 161.8, 141.0, 134.1, 129.4, 124.8, 117.2, 23.5; IR ($CDCl_3$) 3155, 2984, 1641, 1470, 1382, 1096 cm^{-1}; mass spectrum (CI) *m/z* 269.0816 [$C_{16}H_{13}O_4$ (M+1) requires 269.0814] (base), 253.

NMR Assignments. ^{1}H NMR (500 MHz) δ 13.40 (s, 2 H, OH), 7.43 (d, *J* = 8.7 Hz, 2 H, C5-H or C6-H), 7.19 (d, *J* = 8.7 Hz, 2 H, C5-H or C6-H), 2.72 (s, 6 H, C8-H);

^{13}C NMR (125 MHz) δ 190.6 (C1), 161.8 (C7), 141.0, 134.1, 129.4, 124.8, 117.2, 23.5 (C8).

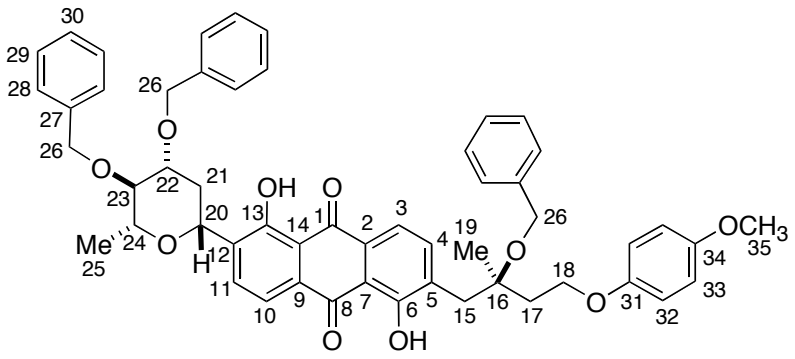


4.76

General procedure of cyloaddition for synthesis of cycloadduct (4.76) [Notebook CLC5-289, 5-88]. Tetrabromide **4.75** (800 mg, 0.60 mmol), which had been dried in the bulb of a Kügelrohr apparatus under vacuum for 2 h at 140 °C, was dissolved in Et_2O (30 mL), and a solution of *n*-BuLi (7.8 mL of a 0.23 M solution, 1.84 mmol, which was prepared by diluting 0.8 mL of 2.3 M *n*-BuLi in hexanes with 7.0 mL Et_2O) was added dropwise (30 min) at –20 °C. Once the addition was complete, the reaction was stirred for 10 min at –20 °C. The mixture was quenched with EtOH (1 mL) and then poured onto saturated $NaHCO_3$ (30 mL) and Et_2O (300 mL). The organic layer was separated, washed with saturated $NaHCO_3$ (3 x 30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (1:4) to afford 517 mg (85%) of a mixture of diastereomeric cycloadducts **4.76** as a yellowish oil. ^{1}H NMR (400 MHz) of an enriched diastereomer δ 7.35-7.20 (m, 15 H), 6.99 (s, 1 H), 6.82-6.70 (m, 5 H), 5.74-5.71 (m, 2 H), 4.98 (d, *J* = 11.0 Hz, 1 H), 4.69 (d, *J* = 11.6 Hz, 1 H), 4.66 (d, *J* = 11.0 Hz, 1 H), 4.59 (d, *J*= 11.6 Hz,

1 H), 4.60-4.45 (m, 3 H), 4.37 (d, *J* = 10.8 Hz, 1 H), 4.25 (d, *J* = 10.8 Hz, 1 H), 4.00-3.81 (m, 4 H), 3.76 (s, 3 H), 3.66-3.58 (m, 1 H), 3.42-3.35 (m, 1 H), 3.14 (t, *J* = 9.0 Hz, 1 H), 2.76 (d, *J* = 18.4 Hz, 1 H), 2.49 (d, *J* = 18.6 Hz, 1 H), 2.26 (dd, *J* = 11.8, 4.2 Hz, 1 H), 2.12-1.98 (m, 2 H), 1.72-1.62 (m, 1 H), 1.53-1.43 (m, 1 H), 1.40 (s, 3 H), 1.36 (d, *J* = 6.0 Hz, 3 H), 1.27-1.17 (m, 1 H), 1.12-1.03 (m, 2 H), 0.36 (s, 3 H), 0.33 (s, 3 H), 0.16 (s, 3 H), 0.06 (s, 3 H); IR (NaCl) 2936, 2878, 1507, 1454, 1229, 1109, 1038, cm^{-1}; mass spectrum (CI) *m/z* 1019.4559 [$C_{61}H_{70}O_{10}Si_2$ (M+1) requires 1019.4585] (base), 992, 885, 694.

NMR Assignments. ^{1}H NMR (400 MHz) of an enriched diastereomer δ 7.35-7.20 (m, 15 H, C20-H, C21-H & C22-H), 6.99 (s, 1 H, C4-H), 6.82-6.70 (m, 5 H, C4-H, C10-H & C11-H), 5.74-5.71 (m, 2 H, C5-H), 4.98 (d, *J* = 11.0 Hz, 1 H, C14-H), 4.69 (d, *J* = 11.6 Hz, 1 H, C13-H), 4.66 (d, *J* = 11.0 Hz, 1 H, C13-H), 4.59 (d, *J*= 11.6 Hz, 1 H, C13-H), 4.60-4.45 (m, 3 H, C13-H), 4.37 (d, *J* = 10.8 Hz, 1 H, C9-H), 4.25 (d, *J* = 10.8 Hz, 1 H, C9-H), 4.00-3.81 (m, 4 H, C3-H), 3.76 (s, 3 H, C12-H), 3.66-3.58 (m, 1 H, C16-H), 3.42-3.35 (m, 1 H, C18-H), 3.14 (t, *J* = 9.0 Hz, 1 H, C17-H), 2.76 (d, *J* = 18.4 Hz, 1 H, C6-H), 2.49 (d, *J* = 18.6 Hz, 1 H, C6-H), 2.26 (dd, *J* = 11.8, 4.2 Hz, 1 H, C15-H), 2.12-1.98 (m, 2 H, C8-H), 1.72-1.62 (m, 1 H, C15-H), 1.53-1.43 (m, 1 H, C2-H), 1.40 (s, 3 H, C7-H), 1.36 (d, *J* = 6.0 Hz, 3 H, C19-H), 1.27-1.17 (m, 1 H, C2-H), 1.12-1.03 (m, 2 H, C2-H), 0.36 (s, 3 H, C1-H), 0.33 (s, 3 H, C1-H), 0.16 (s, 3 H, C1-H), 0.06 (s, 3 H, C1-H).

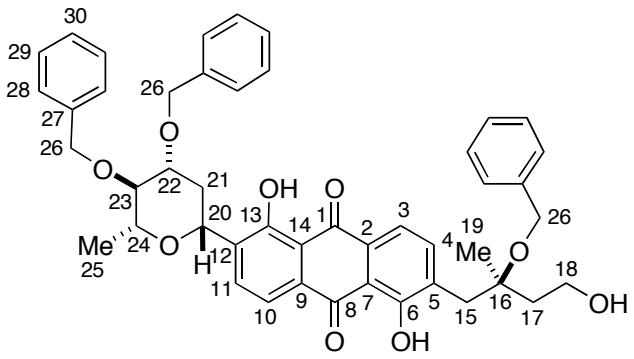


4.77

Anthraquinone (4.77) [Notebook CLC5-201, CLC5-205, CLC5-235, CLC5-236]. Potassium hydroxide (10 pellets) and H_2O (1 mL) were added to a solution of cycloadduct **4.76** (260 mg, 0.25 mmol) in DMF (10 mL), and the mixture was stirred for 24 h at room temperature. A mixture of 50% Et_2O/hexanes (200 mL) was added, and the solution was washed with brine (5 x 10 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOH (27 mL), and concentrated hydrochloric acid (41 drops) was added. The rection was stirred for 4 h at 70 ºC and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (8:1) to afford 74 mg (34%) of **4.77** as a yellowish oil. ^{1}H NMR (500 MHz) δ 13.19 (s, 1 H, OH), 13.11 (s, 1 H, OH), 7.90 (d, *J* = 7.91 Hz, 1 H), 7.85 (d, *J* = 7.91 Hz, 1 H), 7.74 (d, *J* = 7.78 Hz, 1 H), 7.71 (d, *J* = 7.91 Hz, 1 H), 7.36-7.24 (comp, 15 H), 6.83-6.76 (comp, 4 H), 4.99 (d, *J* = 11.2 Hz, 1 H), 4.86 (dd, *J* = 11.5, 1.7 Hz, 1 H), 4.72 (d, *J* = 8.0 Hz, 1 H), 4.70 (d, *J* = 8.0 Hz, 1 H), 4.64 (d, *J* = 11.2 Hz, 1 H), 4.55 (s, 2 H), 4.17-4.08 (comp, 2 H), 3.85 (ddd, *J* = 13.5, 8.9, 4.7 Hz, 1 H), 3.74 (s, 3 H), 3.57 (dq, *J* = 8.9, 6.2 Hz, 1 H), 3.21 (t, *J* = 8.9 Hz, 1 H), 3.19 (d, *J* = 13.6 Hz, 1 H), 3.11 (d, *J* = 13.6 Hz, 1 H), 2.69 (ddd, *J* = 12.8, 4.7, 1.7 Hz, 1 H), 2.21-2.07 (comp, 2 H), 1.48-1.39 (m, 1 H), 1.39 (d, *J* = 6.2 Hz, 3 H), 1.34 (s, 3 H); ^{13}C NMR (125 MHz) δ 188.3, 188.2, 161.5, 158.9, 153.8, 153.0, 139.4, 139.1, 138.6, 138.5, 138.4, 138.3, 135.5, 133.3,

131.9, 131.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 125.5. 119.4, 118.6, 115.5, 114.7, 84.0, 80.9, 77.5, 75.8, 75.3, 71.4, 71.2, 64.6, 63.8, 55.7, 37.7, 37.4, 37.3, 23.1, 18.6; IR (NaCl) 2918, 2848, 1625, 1507, 1431, 1372, 1284, 1261, 1231, 1107, 1090, 1072 cm^{-1}; mass spectrum (CI) *m/z* 849.3634 [$C_{53}H_{53}O_{10}$ (M+1) requires 849.3639], 742 (base), 726, 419, 293, 267.

NMR Assignments. ^{1}H NMR (500 MHz) δ 13.19 (s, OH, 1 H), 13.11 (s, OH, 1 H), 7.90 (d, *J* = 7.91 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.85 (d, *J* = 7.91 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.74 (d, *J* = 7.78 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.71 (d, *J* = 7.91 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.36-7.24 (comp, 15 H, C28-H, C29-H & C30-H), 6.83-6.76 (comp, 4 H, C32-H & C33-H), 4.99 (d, *J* = 11.2 Hz, 1 H, C26-H), 4.86 (dd, *J* = 11.5, 1.7 Hz, 1 H, C20-H), 4.72 (d, *J* = 8.0 Hz, 1 H, C26-H), 4.70 (d, *J* = 8.0 Hz, 1 H, C26-H), 4.64 (d, *J* = 11.2 Hz, 1 H, C26-H), 4.55 (s, 2 H, C26-H), 4.17-4.08 (comp, 2 H, C18-H), 3.85 (ddd, *J* = 13.5, 8.9, 4.7 Hz, 1 H, C22-H), 3.74 (s, 3 H, C35-H), 3.57 (dq, *J* = 8.9, 6.2 Hz, 1 H, C24-H), 3.21 (t, *J* = 8.9 Hz, 1 H, C23-H), 3.19 (d, *J* = 13.6 Hz, 1 H, C15-H), 3.11 (d, *J* = 13.6 Hz, 1 H, C15-H), 2.69 (ddd, *J* = 12.8, 4.7, 1.7 Hz, 1 H, C21-H), 2.21-2.07 (comp, 2 H, C17-H), 1.48-1.39 (m, 1 H, C21-H), 1.39 (d, *J* = 6.2 Hz, 3 H, C25-H), 1.34 (s, 3 H, C19-H); ^{13}C NMR (125 MHz) δ 188.3 (C1 or C8), 188.2 (C1 or C8), 161.5 (C13), 158.9 (C6), 153.8 (C31), 153.0 (C34), 139.4 (C3, C4, C10 or C11), 139.3 (C3, C4, C10 or C11), 119.4 (C3, C4, C10 or C11), 118.6 (C3, C4, C10 or C11), 84.0 (C23), 80.9 (C22), 77.5 (C16), 75.8 (C24), 75.3 (C26), 71.4 (C26), 71.2 (C20), 64.6 (C18), 63.8 (C26), 55.7 (C35), 37.7 (C17), 37.4 (C15), 37.3 (C21), 23.1 (C19), 18.6 (C25); other aromatic carbons: 139.1, 138.6, 138.5, 138.4, 138.3, 135.5, 131.9, 131.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 125.5, 115.5, 114.7.

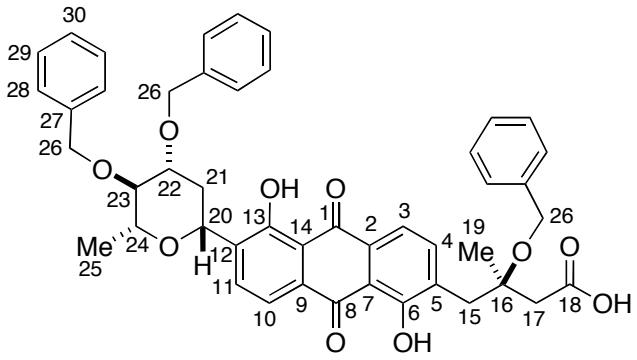


4.162

Anthraquinone (4.162) [Notebook CLC5-203]. A solution of cerium ammonium nitrate (48 mg, 0.09 mmol) in H_2O (0.1 mL) was added to a solution of **4.77** (25 mg, 0.03 mmol) in CH_3CN (2.9 mL) at -15 ºC, and the reaction was stirred for 20 min. Et_2O (20 mL) was added, and the mixture was washed with brine (4 x 3 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (2:1) to afford 16 mg (74%) of **4.162** as a yellowish oil. ^{1}H NMR (500 MHz) δ 13.22 (s, 1 H, OH), 13.09 (s, 1 H, OH), 7.91 (d, *J* = 7.82 Hz, 1 H), 7.85 (d, *J* = 7.82 Hz, 1 H), 7.75 (d, *J* = 7.82 Hz, 1 H), 7.63 (d, *J* = 7.82 Hz, 1 H), 7.36-7.24 (comp, 15 H), 4.99 (d, *J* = 11.3 Hz, 1 H), 4.86 (dd, *J* = 11.4, 1.9 Hz, 1 H), 4.72 (d, *J* = 7.1 Hz, 1 H), 4.70 (d, *J* = 7.1 Hz, 1 H), 4.64 (d, *J* = 11.3 Hz, 1 H), 4.61 (d, *J* = 11.1 Hz, 1 H), 4.58 (d, *J* = 11.1 Hz, 1 H), 3.91-3.80 (comp, 3 H), 3.57 (dq, *J* = 9.1, 6.1 Hz, 1 H), 3.21 (t, *J* = 9.1 Hz, 1 H), 3.18 (d, *J* = 13.6 Hz, 1 H), 3.12 (d, *J* = 13.6 Hz, 1 H), 2.69 (ddd, *J* = 13.0, 5.1, 1.9 Hz, 1 H), 2.62 (t, *J* = 4.8 Hz, 1 H, OH), 1.98-1.90 (m, 1 H), 1.88-1.82 (m, 1 H), 1.48-1.39 (m, 1 H), 1.39 (s, 3 H), 1.38 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz) δ 188.2, 161.5, 158.9, 139.2, 138.6, 138.5, 138.4, 138.3, 135.1, 133.3, 131.8, 131.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 119.4, 118.7, 115.6, 115.5, 84.0, 80.8, 79.6, 75.8, 75.3, 71.4, 71.2, 64.1, 59.4, 40.3, 37.3, 36.9, 22.8, 18.6; IR (NaCl) 3428 (br), 2930, 2872, 1626, 1606, 1582, 1475, 1431, 1372,

1318, 1279, 1260, 1109, 1090, 1071 cm^{-1}; mass spectrum (CI) *m/z* 741.3059 [$C_{46}H_{45}O_9$ (M-1) requires 741.3064] (base), 633.

NMR Assignments. ^1H NMR (500 MHz) δ 13.22 (s, OH, 1 H), 13.09 (s, OH, 1 H), 7.91 (d, *J* = 7.82 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.85 (d, *J* = 7.82 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.75 (d, *J* = 7.82 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.63 (d, *J* = 7.82 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.36-7.24 (comp, 15 H, C28-H, C29-H & C30-H), 4.99 (d, *J* = 11.3 Hz, 1 H, C26-H), 4.86 (dd, *J* = 11.4, 1.9 Hz, 1 H, C20-H), 4.72 (d, *J* = 7.1 Hz, 1 H, C26-H), 4.70 (d, *J* = 7.1 Hz, 1 H, C26-H), 4.64 (d, *J* = 11.3 Hz, 1 H, C26-H), 4.61 (d, *J* = 11.1 Hz, 1 H, C26-H), 4.58 (d, *J* = 11.1 Hz, 1 H, C26-H), 3.91-3.80 (comp, 3 H, C18-H & C22-H), 3.57 (dq, *J* = 9.1, 6.1 Hz, 1 H, C24-H), 3.21 (t, *J* = 9.1 Hz, 1 H, C23-H), 3.18 (d, *J* = 13.6 Hz, 1 H, C15-H), 3.12 (d, *J* = 13.6 Hz, 1 H, C15-H), 2.69 (ddd, *J* = 13.0, 5.1, 1.9 Hz, 1 H, C21-H), 2.62 (t, *J* = 4.8 Hz, 1 H, OH), 1.98-1.90 (m, 1 H, C17-H), 1.88-1.82 (m, 1 H, C17-H), 1.48-1.39 (m, 1 H, C21-H), 1.39 (s, 3 H, C19-H), 1.38 (d, *J* = 6.1 Hz, 3 H, C25-H); ^{13}C NMR (125 MHz) δ 188.2 (C1 & C8), 161.5 (C13), 158.9 (C6), 139.2 (C3, C4, C10 or C11), 133.3 (C3, C4, C10 or C11), 119.4 (C3, C4, C10 or C11), 118.7 (C3, C4, C10 or C11), 84.0 (C23), 80.8 (C22), 79.6 (C16), 75.8 (C24), 75.3 (C26), 71.4 (C26), 71.2 (C20), 64.1 (C26), 59.4 (C18), 40.3 (C17), 37.3 (C21), 36.9 (C15), 22.8 (C19), 18.6 (C25); other aromatic carbons: 138.6, 138.5, 138.4, 138.3, 135.1, 131.8, 131.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 115.6, 115.5.

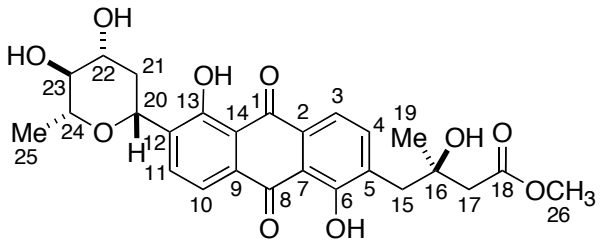


4.163

Anthraquinone (4.163) [Notebook CLC5-292, CLC5-293]. IBX (9 mg, 0.03 mmol) was added to a solution of alcohol **4.162** (8.0 mg, 0.01 mmol) in EtOAc (1 mL), and the resulting suspension was stirred for 3 h at 80 °C. The reaction was allowed to cool to room temperature, and Et_2O (5 mL) was added. The mixture was filtered through a pad of celite, and the filtrate was concentrated under reduced pressure. The crude aldehyde thus obtained was dissolved in *t*-BuOH-H_2O (3.5:1, 2 mL), and the solution was cooled to 0 °C. $NaH_2PO_4 \bullet 2H_2O$ (28 mg, 0.18 mmol), 2-methyl-2-butene (0.16 mL, 1.51 mmol), and $NaClO_2$ (21 mg, 0.23 mmol) were then added, and the mixture was stirred for 90 min at room temperature. The mixture was diluted with Et_2O (20 mL) and washed with brine (3 x 2 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (1:2) to afford 5.7 mg (70%) of acid **4.163** as a yellowish oil. ^{1}H NMR (500 MHz) δ 13.24 (s, 1 H, OH), 13.05 (s, 1 H, OH), 9.80 (br, 1 H), 7.91 (d, *J* = 7.91 Hz, 1 H), 7.85 (d, *J* = 7.77 Hz, 1 H), 7.78 (d, *J* = 7.76 Hz, 1 H), 7.63 (d, *J* = 7.76 Hz, 1 H), 7.38-7.25 (comp, 15 H), 4.99 (d, *J* = 11.0 Hz, 1 H), 4.86 (dd, *J* = 11.3, 1.3 Hz, 1 H), 4.74-4.62 (comp, 5 H), 3.85 (ddd, *J* = 13.6, 8.6, 4.9 Hz, 1 H), 3.57 (dq, *J* = 8.8, 6.1 Hz, 1 H), 3.29 (d, *J* = 13.6 Hz, 1 H), 3.21 (t, *J* = 8.8 Hz, 1 H), 3.18 (d, *J* = 13.6 Hz, 1 H), 2.71 (d, *J* = 15.3 Hz, 1 H), 2.71-2.67 (comp, 1 H), 2.66 (d, *J* = 15.3 Hz, 1 H), 1.49 (s, 3 H), 1.48-1.40 (m, 1 H), 1.39

(d, J = 6.1 Hz, 3 H); ^{13}C NMR (125 MHz) δ 188.2, 188.1, 171.1, 161.4, 159.0, 139.2, 138.7, 138.6, 138.5, 137.2, 133.6, 133.4, 132.1, 131.7, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 119.6, 118.8, 115.8, 115.4, 83.9, 80.8, 78.2, 75.8, 75.3, 71.4, 71.2, 64.9, 44.1, 37.3, 36.8, 22.7, 18.6; IR (NaCl) 2919, 2860, 1702, 1619, 1431, 1366, 1320, 1290, 1255, 1114, 1091, 1073 cm^{-1}; mass spectrum (CI) m/z 757.3013 [$C_{46}H_{45}O_{10}$ (M+1) requires 757.3013], 689, 621, 502 (base), 458, 355.

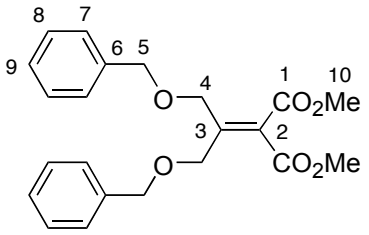
NMR Assignments. ^{1}H NMR (500 MHz) δ 13.24 (s, OH, 1 H), 13.05 (s, OH, 1 H), 9.80 (br, 1 H, COOH), 7.91 (d, J = 7.91 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.85 (d, J = 7.77 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.78 (d, J = 7.76 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.63 (d, J = 7.76 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.38-7.25 (comp, 15 H, C28-H, C29-H & C30-H), 4.99 (d, J = 11.0 Hz, 1 H, C26-H), 4.86 (dd, J = 11.3, 1.3 Hz, 1 H, C20-H), 4.74-4.62 (comp, 5 H, C26-H), 3.85 (ddd, J = 13.6, 8.6, 4.9 Hz, 1 H, C22-H), 3.57 (dq, J = 8.8, 6.1 Hz, 1 H, C24-H), 3.29 (d, J = 13.6 Hz, 1 H, C15-H), 3.21 (t, J = 8.8 Hz, 1 H, C23-H), 3.18 (d, J = 13.6 Hz, 1 H, C15-H), 2.71 (d, J = 15.3 Hz, 1 H, C17-H), 2.71-2.67 (comp, 1 H, C21-H), 2.66 (d, J = 15.3 Hz, 1 H, C17-H), 1.49 (s, 3 H, C19-H), 1.48-1.40 (m, 1 H, C21-H), 1.39 (d, J = 6.1 Hz, 3 H, C25-H); ^{13}C NMR (125 MHz) δ 188.2 (C1 or C8), 188.1 (C1 or C8), 171.1 (C18), 161.4 (C13), 159.0 (C6), 139.2 (C3, C4, C10 or C11), 133.4 (C3, C4, C10 or C11), 119.6 (C3, C4, C10 or C11), 118.8 (C3, C4, C10 or C11), 83.9 (C23), 80.8 (C22), 78.2 (C16), 75.8 (C24), 75.3 (C26), 71.4 (C26), 71.2 (C20), 64.9 (C26), 44.1 (C17), 37.3 (C21), 36.8 (C15), 22.7 (C19), 18.6 (C25); other aromatic carbons: 138.7, 138.6, 138.5, 137.2, 133.6, 132.1, 131.7, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 115.8, 115.4.



4.1

Vineomycinone B_2 Methyl Ester (4.1) [Notebook CLC5-294]. BBr_3 in CH_2Cl_2 (1 M, 0.2 mL, 0.2 mmol) was added to a solution of acid **4.163** (5.5 mg, 7.27 μmol) in CH_2Cl_2 (2 mL) at -78 ºC. The mixture was stirred for 10 min at -78 ºC, and methanolic HCl (2 mL, prepared by addition of 0.2 mL of AcCl to 5 mL of MeOH) was added. The mixture was stirred for 6 h at room temperature and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluting with EtOAc to afford 2.6 mg (71%) of vineomycinone B_2 methyl ester **(4.1)** as an orange solid; mp 183-184 ºC (lit.[143d] mp 183-184 ºC); $[\alpha]^{24}_D$ +109.5 (c 0.00091, $CDCl_3$) [lit.[143d] $[\alpha]_D$ +109.1 (c 0.00066, $CDCl_3$)]; ^{1}H NMR (500 MHz) δ 13.20 (s, 1 H, OH), 13.09 (s, 1 H, OH), 7.90 (d, *J* = 7.91 Hz, 1 H), 7.85 (d, *J* = 7.91 Hz, 1 H), 7.80 (d, *J* = 7.77 Hz, 1 H), 7.68 (d, *J* = 7.91 Hz, 1 H), 4.94 (dd, *J* = 11.3, 1.8 Hz, 1 H), 3.87 (s, 1 H, OH), 3.86-3.81 (m, 1 H), 3.70 (s, 3H), 3.52 (dq, *J* = 9.0, 6.1 Hz, 1 H), 3.21 (dt, *J* = 9.0, 3.5 Hz, 1 H), 3.09 (d, *J* = 13.4 Hz, 1 H), 3.01 (d, *J* = 13.4 Hz, 1 H), 2.57 (d, *J* = 16.0 Hz, 1 H), 2.53 (d, *J* = 16.0 Hz, 1 H), 2.52 (ddd, *J* = 12.7, 4.8, 1.8 Hz, 1 H), 2.20 (d, *J* = 3.5 Hz, 1 H, OH), 2.10 (d, *J* = 3.7 Hz, 1 H, OH), 1.52-1.42 (m, 1 H), 1.41 (d, *J* = 6.1 Hz, 3 H), 1.29 (s, 3 H); ^{13}C NMR (125 MHz) δ 188.2, 188.2, 173.3, 161.4, 159.0, 139.6, 138.3, 134.7, 133.3, 131.9, 131.8, 119.4, 118.9, 115.6, 115.5, 78.1, 75.9, 73.1, 71.8, 71.3, 51.7, 44.4, 40.5, 39.4, 27.3, 18.1; IR (NaCl) 3400 (br), 2930, 2860, 1733, 1626, 1433, 1374, 1260, 1090, 1070, 993, 971 cm^{-1}; mass spectrum (CI) *m/z* 501.1757 [$C_{26}H_{29}O_{10}$ (M+1) requires 501.1761] (base), 326.

NMR Assignments. ^{1}H NMR (500 MHz) δ 13.20 (s, 1 H, OH), 13.09 (s, 1 H, OH), 7.90 (d, *J* = 7.91 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.85 (d, *J* = 7.91 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.80 (d, *J* = 7.77 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 7.68 (d, *J* = 7.91 Hz, 1 H, C3-H, C4-H, C10-H, or C11-H), 4.94 (dd, *J* = 11.3, 1.8 Hz, 1 H, C20-H), 3.87 (s, 1 H, OH), 3.86-3.81 (m, 1 H, C22-H), 3.70 (s, 3 H, C26-H), 3.52 (dq, *J* = 9.2, 6.2 Hz, 1 H, C24-H), 3.21 (dt, *J* = 9.0, 3.5 Hz, 1 H, C23-H), 3.09 (d, *J* = 13.4 Hz, 1 H, C15-H), 3.01 (d, *J* = 13.4 Hz, 1 H, C15-H), 2.57 (d, *J* = 16.0 Hz, 1 H, C17-H), 2.53 (d, *J* = 16.0 Hz, 1 H, C17-H), 2.52 (ddd, *J* = 12.7, 4.8, 1.8 Hz, 1 H, C21-H), 2.20 (d, *J* = 3.5 Hz, 1 H, OH), 2.10 (d, *J* = 3.7 Hz, 1 H, OH), 1.52-1.42 (m, 1 H, C21-H), 1.41 (d, *J* = 6.1 Hz, 3 H, C25-H), 1.29 (s, 3 H, C19-H); ^{13}C NMR (125 MHz) δ 188.23 (C1 or C8), 188.17 (C1 or C8), 173.29 (C18), 161.36 (C13), 158.98 (C6), 139.61 (C3, C4, C10 or C11), 133.33 (C3-H, C4-H, C10-H, or C11-H), 119.41 (C3-H, C4-H, C10-H, or C11-H), 118.90 (C3-H, C4-H, C10-H, or C11-H), 78.07 (C23), 75.93 (C24), 73.14 (C22), 71.82 (C20), 71.27 (C16), 51.73 (C26), 44.40 (C17), 40.50 (C15), 39.39 (C21), 27.28 (C19), 18.11 (C25); other aromatic carbons: 138.28, 134.72, 131.89, 131.81, 115.63, 115.50.

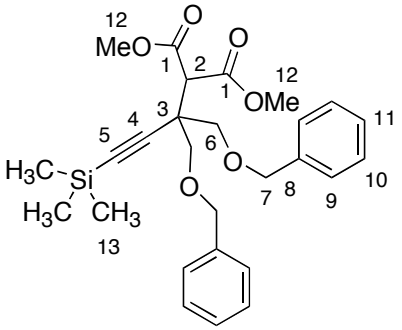


5.15

2-(2-Benzyloxy-1-benzyloxymethyl-ethylidene)-malonic acid dimethyl ester (5.15) [Notebook CLC6-137]. A solution of $TiCl_4$ (464 μL, 4.26 mmol) in CH_2Cl_2 (5.5 mL) was added dropwise to dry THF (12.5 mL) at 0 ºC. A solution containing the ketone

5.54 (500 mg, 1.85 mmol) and dimethyl malonate (211 μL, 1.85 mmol) in dry THF (12.5 ml) was added dropwise to the $TiCl_4$ solution over three min in an ice bath. After 10 min of stirring, pyridine (0.75 mL, 9.25 mmol) was added. The ice bath was removed, and the reaction was allowed to warm up to room temperature and stirred for 24 h. The mixture was diluted with EtOAc/Hexanes (1:6, 150 mL) and washed with brine (3 x 50 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (10:1) to afford 609 mg (86%) of **5.15** as a yellowish oil. ^{1}H NMR (400 MHz) δ 7.37-7.24 (comp, 10 H), 4.48 (s, 4 H), 4.46 (s, 4 H), 3.65 (s, 6 H); ^{13}C NMR (100 MHz) δ 52.3, 67.8, 73.2, 125.9, 127.8, 127.8, 128.4, 137.6, 153.4, 165.2; IR ($CDCl_3$) 3030, 2916, 2849, 1726, 1452, 1433, 1229, 1054, 1040 cm^{-1}; mass spectrum (CI) *m/z* 385.1655 [$C_{22}H_{25}O_6$ (M+1) requires 385.1651], 354, 277 (base), 181.

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.37-7.24 (comp, 10 H, C7-H, C8-H and C9-H), 4.48 (s, 4 H, C4-H or C5-H), 4.46 (s, 4 H, C4-H or C5-H), 3.65 (s, 6 H, C10-H); ^{13}C NMR (100 MHz) δ 52.3 (C10), 67.8 (C4), 73.2 (C5), 125.9 (C2), 127.8 (C7, C8 or C9), 127.8 (C7, C8 or C9), 128.4 (C7, C8 or C9), 137.6 (C6), 153.4 (C3), 165.2 (C1).

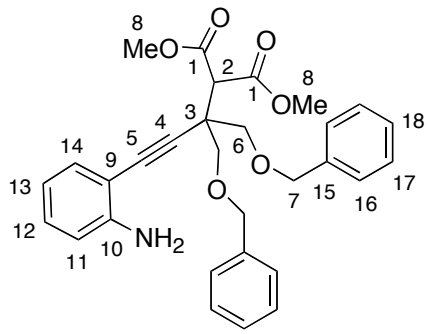


5.72

2-[1,1-Bis-benzyloxymethyl-3-(trimethyl-silanyl)-prop-2-ynyl]-malonic acid

dimethyl ester (5.72) [Notebook CLC6-197 and CLC6-228]. A solution of trimethylsilylacetylene (4.0 mL, 28.0 mmol) in Et_2O (50 mL) was added *n*-BuLi (11.3 mL of a 2.07 M solution in hexanes, 23.4 mmol) at –78 °C, and the reaction was stirred for 1 h at 10 °C. CuI (2.24 g, 11.8 mmol) was added, and the reaction was stirred for 1 h to give a pale yellow solution of lithium diethynylcuprate **5.71** (0.18 M solution in Et_2O). A solution of **5.71** (62 mL of a 0.18 M solution in Et_2O, 11.1 mmol) was added to a solution of ester **5.15** (2.85 g, 7.42 mmol) in Et_2O (62 mL) over 3 min at 0 ^oC, and the reaction was stirred for 48 h at 0 ^oC. The reaction was allowed to warm up to room temperature and stirred for another 12 h. The mixture was diluted with hexanes (200 mL) and washed with brine (2 x 200 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (15:1) to afford 1.87 g (52%) of **5.72** as a yellowish oil. ^1H NMR (400 MHz) δ 7.20-7.08 (comp, 10 H), 4.43 (d, *J* = 12.0 Hz, 2 H), 4.40 (d, *J* = 12.0 Hz, 2 H), 3.75 (s, 1 H), 3.74 (d, *J* = 9.2 Hz, 2 H), 3.71 (d, *J* = 9.2 Hz, 2 H), 3.47 (s, 6 H); ^{13}C NMR (100 MHz) δ -0.1, 43.8, 52.1, 53.6, 71.2, 73.3, 88.9, 105.0, 127.4, 127.4, 128.2, 138.3, 167.6; IR ($CDCl_3$) 2953, 2863, 1761, 1736, 1454, 1434, 1248, 1105, 1028, 843 cm^{-1}; mass spectrum (CI) *m/z* mass spectrum (CI) *m/z* 483.2204 [$C_{27}H_{35}SiO_6$ (M+1) requires 483.2203](base).

NMR Assignments. ^1H NMR (400 MHz) δ 7.20-7.08 (comp, 10 H, C9-H, C10-H and C11-H), 4.43 (d, *J* = 12.0 Hz, 2 H, C7-H), 4.40 (d, *J* = 12.0 Hz, 2 H, C7-H), 3.75 (s, 1 H, C2-H), 3.74 (d, *J* = 9.2 Hz, 2 H, C6-H), 3.71 (d, *J* = 9.2 Hz, 2 H, C6-H), 3.47 (s, 6 H, C9-H); ^{13}C NMR (100 MHz) δ -0.1 (C13), 43.8 (C3), 52.1 (C2), 53.6 (C12), 71.2 (C6), 73.3 (C7), 88.9 (C5), 105.0 (C4), 127.4 (C9, C10 or C11), 127.4 (C9, C10 or C11), 128.2 (C9, C10 or C11), 138.3 (C8), 167.6 (C1).

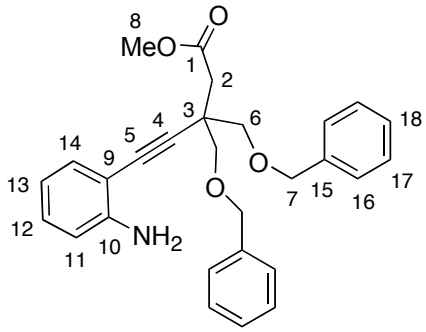


5.74

2-[1,1-Bis-benzyloxymethyl-3-(trimethyl-silanyl)-prop-2-ynyl]-malonic acid dimethyl ester (**5.74**) **[Notebook CLC6-207].** A solution of alkyne **5.72** (1.83 g, 3.79 mmol) and TBAF (1.98 g, 7.58 mmol) in DMF (10 mL) was stirred for 2 h under argon. 2-Iodoaniline (997 mg, 4.55 mmol), $PdCl_2$ (67 mg, 0.38 mmol), PPh_3 (198 mg, 0.76 mmol), CuI (72 mg, 0.38 mmol), and triethylamine (30 mL) were added, and the mixture was sparged with argon for 10 min and stirred for 18 h at room temperature. The reaction mixture was diluted with hexanes/EtOAc (10:1, 300 mL) and washed with brine (4 x 100 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (3:1) to afford 1.64 g (86%) of **5.74** as a yellowish oil. ^{1}H NMR (500 MHz) δ 7.31-7.23 (comp, 10 H), 7.17 (dd, 1 H, *J* = 7.5, 1.6 Hz, 1 H), 7.04 (ddd, *J* = 8.1, 7.5, 1.6 Hz, 1 H), 6.61-6.54 (comp, 2 H), 4.57 (d, *J* = 11.9 Hz, 2 H), 4.53 (d, *J* = 11.9 Hz, 2 H), 4.40 (br, 2 H), 3.96 (s, 1 H), 3.89 (d, *J* = 9.1 Hz, 2 H), 3.87 (d, *J* = 9.1 Hz, 2 H), 3.63 (s, 6 H); ^{13}C NMR (125 MHz) δ 43.8, 52.4, 53.5, 71.6, 73.5, 81.8, 93.1, 107.3, 113.8, 117.0, 127.6, 127.6, 128.3, 129.4, 131.6, 138.1, 149.2, 167.8; IR ($CDCl_3$) 3371, 3028, 2949, 1732, 1620, 1494, 1454, 1314, 1206, 1162, 1101 cm^{-1}; mass spectrum (CI) *m/z* 502.2230 [$C_{30}H_{32}NO_6$ (M+1) requires 502.2230](base), 295.

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.31-7.23 (comp, 10 H, C16-H, C17-

H & C18-H), 7.17 (dd, 1 H, *J* = 7.5, 1.6 Hz, 1 H, C11-H or C14-H), 7.04 (ddd, *J* = 8.1, 7.5, 1.6 Hz, 1 H, C12-H or C13-H), 6.61-6.54 (comp, 2 H, C11-H, C12-H, C13-H or C14-H), 4.57 (d, *J* = 11.9 Hz, 2 H, C7-H), 4.53 (d, *J* = 11.9 Hz, 2 H, C7-H), 4.40 (br, 2 H, NH), 3.96 (s, 1 H, C2-H), 3.89 (d, *J* = 9.1 Hz, 2 H, C6-H), 3.87 (d, *J* = 9.1 Hz, 2 H, C6-H), 3.63 (s, 6 H, C8-H); ^{13}C NMR (125 MHz) δ 43.8 (C3), 52.4 (C2), 53.5 (C8), 71.6 (C6), 73.5 (C7), 81.8 (C5), 93.1 (C4), 107.3 (C9), 113.8 (C11, C12, C13 or C14), 117.0 (C11, C12, C13 or C14), 127.6 (C15, C16, C17 or C18), 127.6 (C15, C16, C17 or C18), 128.3 (C15, C16, C17 or C18), 129.4 (C11, C12, C13 or C14), 131.6 (C11, C12, C13 or C14), 138.1 (C15, C16, C17 or C18), 149.2 (C10), 167.8 (C1).

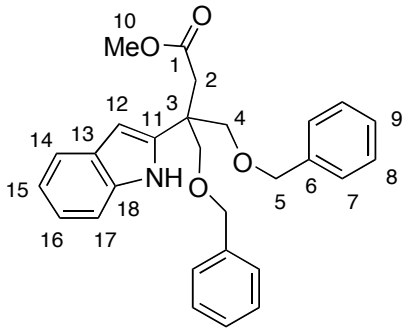


5.76

5-(2-Amino-phenyl)-3,3-bis-benzyloxymethyl-pent-4-ynoic acid methyl ester (5.76) [Notebook CLC6-214]. Sodium cyanide (7 mg, 0.13 mmol) was added to a solution of 2-alkynylaniline **5.74** (32 mg, 0.06 mmol) in DMSO (1 mL), and the reaction was stirred for 2 h at 90 °C. The mixture was allowed to cool to room temperature, diluted with Et_2O (20 mL) and washed with brine (5 x 2 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (3:1) to afford 25 mg (88%) of **5.76** as a yellowish oil. ^{1}H NMR (500 MHz) δ 7.32-7.24 (comp, 10 H), 7.18 (dd, 1 H, *J* =

7.5, 1.6 Hz, 1 H), 7.04 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1 H), 6.61-6.56 (comp, 2 H), 4.58 (d, *J* = 12.4 Hz, 2 H), 4.56 (d, *J* = 12.4 Hz, 2 H), 4.34 (br, 2 H), 3.73 (d, *J* = 9.0 Hz, 2 H), 3.71 (d, *J* = 9.0 Hz, 2 H), 3.62 (s, 3 H), 2.72 (s, 2 H); ^{13}C NMR (125 MHz) δ 38.2, 40.9, 51.6, 72.5, 73.4, 80.8, 95.0, 107.5, 113.9, 117.1, 127.6, 127.6, 128.3, 129.3, 131.6, 138.3, 148.9, 171.5; IR ($CDCl_3$) 3363, 3019, 2949, 2861, 1733, 1618, 1493, 1454, 1360, 1312, 1200, 1101 cm^{-1}; mass spectrum (CI) *m/z* 444.2172 [$C_{28}H_{30}NO_4$ (M+1) requires 444.2175](base), 336.

NMR Assignments. ^{1}H NMR (500 MHz) δ 7.32-7.24 (comp, 10 H, C16-H, C17-H & C18-H), 7.18 (dd, 1 H, *J* = 7.5, 1.6 Hz, 1 H, C11-H or C14-H), 7.04 (ddd, *J* = 8.2, 7.5, 1.6 Hz, 1 H, C12-H or C13-H), 6.61-6.56 (comp, 2 H, C11-H, C12-H, C13-H or C14-H), 4.58 (d, *J* = 12.4 Hz, 2 H, C7-H), 4.56 (d, *J* = 12.4 Hz, 2 H, C7-H), 4.34 (br, 2 H, NH), 3.73 (d, *J* = 9.0 Hz, 2 H, C6-H), 3.71 (d, *J* = 9.0 Hz, 2 H, C6-H), 3.62 (s, 3 H, C8-H), 2.72 (s, 2 H, C2-H); ^{13}C NMR (125 MHz) δ 38.2 (C2), 40.9 (C3), 51.6 (C8), 72.5 (C6), 73.4 (C7), 80.8 (C5), 95.0 (C4), 107.5 (C9), 113.9 (C11, C12, C13 or C14), 117.1 (C11, C12, C13 or C14), 127.6 (C15, C16, C17 or C18), 127.6 (C15, C16, C17 or C18), 128.3 (C15, C16, C17 or C18), 129.3 (C11, C12, C13 or C14), 131.6 (C11, C12, C13 or C14), 138.3 (C15, C16, C17 or C18), 148.9 (C10), 171.5 (C1).

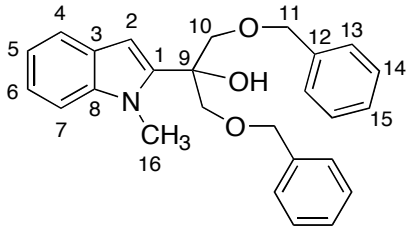


5.77

4-Benzyloxy-3-benzyloxymethyl-3-(1*H*-indol-2-yl)-butyric acid methyl ester (5.77) [Notebook CLC6-217]. $KAuCl_4$ (1 mg) was added to a solution of aniline **5.76** (8 mg, 0.02 mmol) in EtOH (1 mL), and the mixture was stirred for 30 min at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (20:1) to afford 6 mg (75%) of **5.77** as a yellowish oil. ^{1}H NMR (500 MHz) δ 9.29 (br, 1 H), 7.51 (d, *J* = 7.9 Hz, 1 H), 7.35-7.23 (comp, 11 H), 7.09 (t, *J* = 7.5 Hz, 1 H), 7.02 (t, *J* = 7.5 Hz, 1 H), 6.28 (s, 1 H), 4.56 (s, 4 H), 3.96 (d, *J* = 9.0 Hz, 2 H), 3.85 (d, *J* = 9.0 Hz, 2 H), 3.53 (s, 3 H), 2.92 (s, 2 H); ^{13}C NMR (75 MHz) δ 38.4, 43.2, 51.5, 73.3, 73.6, 99.0, 110.8, 119.4, 120.2, 121.4, 127.6, 127.7, 127.8, 128.4, 135.6, 138.0, 140.7, 172.1; IR ($CDCl_3$) 3413, 3029, 2922, 2858, 1732, 1455, 1364, 1300, 1204, 1097 cm^{-1}; mass spectrum (CI) *m/z* 444.2174 [$C_{28}H_{30}NO_4$ (M+1) requires 444.2175], 320, 225 (base).

NMR Assignments. ^{1}H NMR (500 MHz) δ 9.29 (br, 1 H, NH), 7.51 (d, *J* = 7.9 Hz, 1 H, C14-H or C17-H), 7.35-7.23 (comp, 11 H, C7-H, C8-H, C9-H and C14-H or C16-H), 7.09 (t, *J* = 7.5 Hz, 1 H, C15-H or C16-H), 7.02 (t, *J* = 7.5 Hz, 1 H, C15-H or C16-H), 6.28 (s, 1 H, C12-H), 4.56 (s, 4 H, C5-H), 3.96 (d, *J* = 9.0 Hz, 2 H, C4-H), 3.85 (d, *J* = 9.0 Hz, 2 H, C4-H), 3.53 (s, 3 H, C10-H), 2.92 (s, 2 H, C2-H); ^{13}C NMR (75 MHz) δ 38.4 (C2), 43.2 (C3), 51.5 (C10), 73.3 (C4), 73.6 (C5), 99.0 (C12), 110.8 (C14,

C15, C16 or C17), 119.4 (C14, C15, C16 or C17), 120.2 (C14, C15, C16 or C17), 121.4 (C14, C15, C16 or C17), 127.6 (C6, C7, C8 or C9), 127.7 (C6, C7, C8 or C9), 127.8 (C6, C7, C8 or C9), 128.4 (C6, C7, C8 or C9), 135.6 (C11, C13 or C18), 138.0 (C11, C13 or C18), 140.7 (C11, C13 or C18), 172.1 (C1).



5.66

1,3-Dibenzyloxy-2-(1-methyl-1*H*-indol-2-yl)-propan-2-ol (5.66) [Notebook CLC6-183]. A solution of indole **5.65** (112 mg, 0.85 mmol) in Et_2O (1.80 mL) was added TMEDA (107 uL, 0.71 mmol) and *n*-BuLi (0.35 mL of a 2.05 M solution in hexanes, 0.71 mmol) at –78 °C. Once the addition was complete, the reaction was stirred for 30 min in an ice bath and recooled to –78 °C. A solution of ketone **5.54** (154 mg, 0.57 mmol) in Et_2O (1 mL) was added, and the mixture was stirred for 30 min at –78 °C. The reaction was quenched with EtOH (1 mL) and diluted with Et_2O (50 mL). The mixture was washed with brine (3 x 10 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (5:1) to afford 136 mg (60%) of **5.66** as a yellowish oil. ^{1}H NMR (400 MHz) δ ^{1}H NMR (400 MHz) δ 7.57-7.54 (m, 1 H), 7.38-7.18 (comp, 13 H), 6.40 (s, 1 H), 4.58 (s, 4 H), 3.90 (d, *J* = 9.4 Hz, 2 H), 3.86 (d, *J* = 9.4 Hz, 2 H), 3.86 (s, 3 H), 3.19 (s, 1H).

NMR Assignments. ^{1}H NMR (400 MHz) δ 7.57-7.54 (m, 1 H, C5-H), 7.38-7.18 (comp, 13 H, C13-H, C14-H, C15-H, C4-H, C6-H and C7-H), 6.40 (s, 1 H, C2-H), 4.58

(s, 4 H, C11-H), 3.90 (d, J = 9.4 Hz, 2 H, C10-H), 3.86 (d, J = 9.4 Hz, 2 H, C10-H), 3.86 (s, 3 H, C16-H), 3.19 (s, 1H, OH).

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